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# STUDIES OF URINARY PIGMENTS IN PELLAGRA AND OTHER PATHOLOGICAL STATES. I. CLINICAL OBSERVATIONS *

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IN previous communications,[1, 2] one of us (C. J. W.) pointed out that the Ellinger-Dojmi color reaction [3] is due to urorosein, and that porphyrin, although capable of yielding color if present in sufficient amount, was not the source of the positive reactions encountered in urine samples from a variety of conditions, including pellagra. Beckh, Ellinger and Spies [4] had employed the Ellinger-Dojmi reaction for the quantitative estimation of porphyrin in the urine. These investigators reported marked increases of porphyrin in a series of pellagra urines. They stated, moreover, that the administration of nicotinic acid was followed by a prompt fall in the excretion of urinary porphyrin to normal levels. Similar observations were subsequently reported by Sydenstricker, Schmidt, Fulton, New and Geeslin [5] and by Spies and various associates,[6, 7, 8] although in later publications by Spies [9, 10, 11] the pigments responsible for the color reactions were referred to as "porphyrin-like substances." Dobriner and Rhoads [12] and Meiklejohn and Kark [13] have also attested to the non-specificity of the Ellinger-Dojmi reaction for porphyrin, and the latter investigators confirmed the report of Watson [2] that the reaction occurring in pellagra urines is due to urorosein. As a matter of fact, Hunter, Givens, and Lewis [14] in 1919 had noted that urorosein was commonly present in the urine of pellagrins. Since the urorosein reaction may occur in certain urines only after the addition of an oxidizing agent,[2, 13] further investigation was necessary to determine whether the presence of this pigment was correlated in any direct manner with nicotinic acid deficiency.

In addition to positive urorosein reactions, Watson [1, 2] described a red

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pigment resembling indirubin, occurring in the toluene preservatives of urines from pellagrins as well as other patients having deficiency states.

The present study was concerned with the urinary excretion of urorosein and indirubin, or indirubin-like substances in normal human subjects and in patients with nicotinic acid deficiency. Similar studies have also been made of the urine of patients suffering from pathological conditions without clinical evidence of nicotinic acid deficiency.

## Methods and Materials

Urines of eight patients presenting definite clinical evidence of nicotinic acid deficiency were examined daily for the urorosein reaction, for indican, for the presence of an oxidizing agent, and for the development of a red color in the toluene preservatives. The observations were commenced before institution of therapy, and were continued until all clinical evidence of the deficiency had disappeared. The patients had been on diets low in nicotinic acid for appreciable periods, and all of them presented one or more of the manifestations of nicotinic acid deficiency (glossitis, stomatitis, scaling dermatitis, diarrhea, etc.) at the time of admission to the hospital. Five of them suffered, in addition, from anorexia incident to coexisting disease (stricture of the common bile duct, subphrenic abscess following perforation of the gall-bladder, unresolved pneumonia with multiple abscess formation, toxic adenoma of the thyroid, and chronic bronchitis and emphysema.) There was no significant coexisting disease in the remaining three patients, although one suffered from chronic alcoholism. There were five males and three females in the group, and their ages ranged from 51 to 81 years. Two additional 24 hour collections of urine,* one specimen from each of two patients suffering from endemic pellagra, were also examined in this same manner. The porphyrin content of a four day collection of feces from each of these patients was also determined.*

Urines from seven patients receiving deep roentgen therapy for carcinoma of the cervix uteri were examined in a similar manner.† This portion of the study was undertaken because of a report that irradiation sickness was often associated with a positive Beckh-Ellinger-Spies test.[15] The observations were started prior to the institution of the deep roentgen therapy, and were continued during the course of treatment. These women, whose ages ranged from 31 to 65 years, were in the hospital during the entire period of observation. None of them exhibited any clinical evidence of nicotinic acid deficiency. Except when nausea occurred, there was no interference with appetite, and they received the standard hospital diet. No vitamin preparations were given them during this period. The patients were closely

* Study of the urine and feces from these two patients was made possible through the courtesy of Dr. David Smith, Duke University, Durham, N. C.

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observed for development of nausea and vomiting. When this occurred, no specific measures were instituted other than the intravenous administration of 5 per cent glucose in physiological saline when the nausea was severe, or when accompanied by emesis.

The third group of patients consisted of 38 unselected consecutive cases of arthritis as they appeared at the Out-Patient Department. This group was studied because of a report by Lutterloh [16] that the B.E.S. test was commonly positive in cases of arthritis. All of the patients were questioned and examined for symptoms or signs of nicotinic acid deficiency; no evidence of such was present in any. Except for a few instances, the patients had no complaints except those referable to the arthritis. In seven the arthritis was of the atrophic or rheumatoid type; in 30 it was of the hypertrophic variety, and in one it was due to gonorrhea. A single specimen of urine was obtained from each of these patients, and was examined immediately after voiding.

The fourth group consisted of five patients who were admitted to the hospital in severe diabetic acidosis. Spies and co-workers [17] noted frequent positive B.E.S. tests in diabetic acidosis and suggested a correlation with what they believed to be a reduction of codehydrogenase in the blood. One or more specimens of urine were examined (immediately after passage) from each of these patients. None of the patients exhibited any clinical evidence of nicotinic acid deficiency.

The final group consisted of 16 normal individuals. One or more specimens of urine were examined (immediately after voiding) from each of these subjects.

The following procedures were used:

1. Ellinger-Dojmi or Beckh-Ellinger-Spies (B.E.S.) test. This test was carried out in the exact manner described by these authors.[4] A constant amount of urine (10 c.c.) was used in all the determinations.

2. B.E.S. test plus nitrite. One or two drops of a 2 per cent solution of $KNO_2$ were added to 10 c.c. of urine, and the B.E.S. test was then carried out in the usual manner.

3. Nencki-Sieber (N.S.) test.[18] Ten cubic centimeters of urine were strongly acidified with 5 c.c. of 25 per cent HCl, and then extracted with 2 c.c. of primary normal amyl alcohol.

4. N.S. test plus nitrite. One or two drops of a 2 per cent solution of $KNO_2$ were added to 10 c.c. of urine, and the N.S. test was then carried out in the above manner.

It will be noted that the same amounts of urine were used in each of the four tests, so that the intensities of the reactions were comparable. Furthermore, the 25 per cent HCl in the B.E.S. tests and the amyl alcohol in the N.S. tests were examined spectroscopically in order to exclude the possibility that the red color was due to substances other than urorosein.

5. Obermayer's test for indican. Equal parts of urine and Obermayer's reagent were mixed in a test tube, and the indican was then extracted with a small amount of chloroform.

6. Starch-iodine test for nitrite. Six to eight cubic centimeters of urine were acidified with a few cubic centimeters of 2 N $H_2SO_4$. Three to four cubic centimeters of 5 per cent solution of potassium iodide and a few cubic centimeters of a freshly prepared solution of 1 per cent starch were then added. We have found this test sensitive for concentrations of $KNO_2$ as low as 0.0004 gram per 100 c.c.

7. Quantitative determinations of urinary porphyrin were made on the two 24 hour collections of urine from the two patients suffering from endemic pellagra. In the other instances, porphyrin was removed from the acetic acid-ether extract of the urine (in the B.E.S. test) by preliminary extraction with 5 per cent HCl. As was pointed out in a previous report,[2] this extraction with 5 per cent HCl serves to distinguish whether the color reaction in the B.E.S. test is due to porphyrin (removed quantitatively in the 5 per cent HCl) or to urorosein (removed from the acetic-ether extract of urine by the 25 per cent HCl). Coproporphyrin was determined in the 24 hour urines and the four day collections of feces from the two cases of endemic pellagra by means of the following modification of the Fikentscher method.[19]

*Urine:* 100 c.c. were placed in a separatory funnel and strongly acidified with glacial acetic acid. Three extractions with 30 c.c. portions of ether were then carried out. The combined ether was washed twice with small amounts of water and extracted four times with 2 to 3 c.c. portions of 5 per cent HCl. The combined 5 per cent HCl solution was extracted twice with chloroform, after which it was made negative (red) to Congo paper by addition of saturated solution of sodium acetate. The solution was then extracted three times with ether. The combined ether after being washed twice with small amounts of water was extracted four times with 2 c.c. portions of 1 per cent HCl. The amount of coproporphyrin in this final solution was determined by fluorimetry in the usual way,[20] a Zeiss stufenphotometer and a standard coproporphyrin solution being employed.

*Feces:* 10 gm. of the mixed four day collection of feces were ground thoroughly in a mortar with glacial acetic acid and the mixture was then extracted six times with ether. Further small amounts of glacial acetic were added after every other extraction with ether. The acetic and ether extract was poured off in each instance and filtered into a separatory funnel. The combined extract was washed twice with small amounts of water, then extracted repeatedly with 5 per cent HCl. This was continued until the extract no longer exhibited any appreciable red fluorescence in ultraviolet light (carbon arc fitted with Corning red purple ultra filter). The 5 per cent HCl was then made negative to Congo paper by addition of a saturated sodium acetate solution, and three extractions with ether were carried out. The ether was washed twice with water and was then extracted five to seven times with 2 c.c.

portions of 1 per cent HCl (the number of extractions being determined by the removal of red fluorescence). The combined 1 per cent HCl was washed twice with ether which was added to the ether which had just been extracted. This removes small amounts of protoporphyrin which were entrained during the extraction with 1 per cent HCl. The combined ether was then extracted five times with 2 c.c. portions of 5 per cent HCl. This constituted the final protoporphyrin fraction. The 1 per cent HCl fraction was then diluted to 0.2 per cent and extracted repeatedly with chloroform, again determining the number of extractions by means of the red fluorescence. After dilution of the chloroform with four volumes of ether any porphyrin contained was removed by repeated extraction with 1 per cent HCl. This constituted the final "deutero" fraction which includes both deutero and pseudodeuteroporphyrins.[21] The 0.2 per cent HCl remaining after the above chloroform extraction was made negative to Congo paper by addition of sodium acetate solution, after which it was extracted three times with ether. The latter was washed in the usual way and was then extracted four or more times, depending on fluorescence, with 2 c.c. portions of 1 per cent HCl. This was the final coproporphyrin solution. The red fluorescence of the proto-, deutero-, and coproporphyrin fractions was then measured in the usual way by comparison with a standard coproporphyrin solution in 1 per cent HCl, in the stufenphotometer.[20]

8. Toluene was added to a portion of each 24 hour specimen of urine. This portion was then set aside for a period of at least three weeks, and observed for the development of a red color in the toluene layer. During this period the B.E.S. and indican tests were repeated in many of the urines, especially if the toluene became pink or red. All of the toluene preservatives which became pink or red were eventually pooled and were concentrated in vacuo to a very small volume. The various pigments present were then separated by chromatographic analysis. The results of this part of the study will be described separately.

## Results

*Patients Having Nicotinic Acid Deficiency.* Positive spontaneous urorosein reactions (without addition of nitrite) in urines examined immediately after voiding have been noted at one time or another in each of the eight cases of nicotinic acid deficiency. The spontaneous urorosein reaction was often positive during the period of relapse, but it was often noted to disappear prior to the administration of nicotinic acid, and to reappear (even in specimens examined immediately after voiding) long after adequate amounts of nicotinic acid had caused regression of all signs of deficiency (table 1).

Following the addition of nitrite, the urorosein reaction was observed in all but three of 224 urines examined from the eight patients having a deficiency of nicotinic acid (table 2). It did not appear that the amount of the chromogen of urorosein excreted daily in the urine was influenced by the

TABLE I

Summary of Data from Patient Having Alcoholic Pellagra, Showing Absence of Correlation Between B.E.S. Test and Clinical Evidence of Nicotinic Acid Deficiency.*

| Dates | B.E.S. | B.E.S. plus $KNO_2$ | N.S. | N.S. plus $KNO_2$ | Obermayer | Nitrite | Toluene (observed for three weeks) | Diet | Nicotinic Acid mg. (daily) | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | I.V. | Orally | |
| 6–15 to 6–21 | Neg. | + | Neg. | + | Neg. or + | Neg. | Clear | Low vitamin B | — | — | Tongue red and atrophic. Symmetrical brown scaling pigmentation of both hands and wrists. |
| 6–22 to 6–30 | Neg. | + | Neg. | + | Neg. or + | Neg. | Clear | Low vitamin B | 100 | 300 | |
| 7–1 to 7–17 | Neg. | + | Neg. | + | Neg. or + | Neg. | Clear | High vitamin 3000 calories | 100 | 300 | 7–17: All clinical evidence of pellagra has disappeared. |
| 7–18 | + | + | + | + | Neg. | Neg. | Clear | High vitamin 3000 calories | 100 | 300 | |
| 7–19 | + | + | + | + | + | + | Clear | High vitamin 3000 calories | 100 | 300 | |
| 7–20 to 7–21 | Neg. | + | Neg. | + | + | Neg. | Clear | High vitamin 3000 calories | 100 | 300 | 7–21: Patient discharged. No clinical evidence of pellagra. |

* Study of this patient was made possible through the coöperation of Dr. George E. Fahr of the Minneapolis General Hospital.

administration of nicotinic acid. No quantitative measurements were made, but since all the tests were performed using the same amount of urine and reagents, the intensities of the reactions were comparable. The administration of thiamin, and in one instance, of riboflavin, did not influence the presence or the intensity of the reaction.

Herter [22] demonstrated that the urorosein reaction of Nencki and Sieber was produced by the oxidation of indolacetic acid, and it is probable that indolacetic acid is the chromogen of the red pigment which develops in the 25 per cent HCl in the B.E.S. test.[2] Correspondingly, the results of the B.E.S. and N.S. tests in the 224 urines from the eight patients with nicotinic acid deficiency were in agreement in all instances.

In order to identify the urorosein reaction with greater certainty, the 25 per cent HCl in the B.E.S test and the amyl alcohol in the N.S. test were

TABLE II

Summary of the Results of the Tests for Urinary Pigments in the Five Groups of Patients Examined.

| Type of Case | Number of Patients | Total Number of Determinations | Test Positive Without Addition of Nitrite | | Test Positive Only Following Addition of Nitrite | | Test Negative Following Addition of Nitrite | | Urinary Indican | | Starch-Iodine Test Positive for Nitrite | Development of Red Color in Toluene Preservative |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | B.E.S. | N.S. | B.E.S. | N.S. | B.E.S. | N.S. | Neg. or + | ++ to ++++ | | |
| Nicotinic acid deficiency | 8 | 224 | 72 | 72 | 149 | 149 | 3 | 3 | 175 | 49 | 42 | 72 |
| Squamous cell carcinoma of cervix uteri, receiving deep roentgen therapy | 7 | 173 | 10 | 10 | 28 | 28 | 135 | 135 | 169 | 4 | 14 | 60 |
| Arthritis | 38 | 38 | 1 | 1 | 35 | 35 | 2 | 2 | 32 | 6 | 0 | 0 |
| Diabetic acidosis | 5 | 8 | 0 | 0 | 7 | 7 | 1 | 1 | 8 | 0 | 0 | 0 |
| Normals | 16 | 34 | 0 | 0 | 19 | 19 | 15 | 15 | 30 | 4 | 0 | 0 |

examined spectroscopically on repeated occasions in each case. The absorption of urorosein in 25 per cent HCl (B.E.S. test) is characterized by a relatively weak, broad, diffuse band, having its maximum absorption at 543 to 544 mμ. A second weaker band is present at 511 mμ. In every urine in which the B.E.S. test was positive, either spontaneously or following the addition of nitrite, this characteristic absorption was present. The addition of nitrite to urine which gave a positive test spontaneously did not alter the spectroscopic absorption. When urorosein is concentrated in amyl alcohol in the N.S. test, it exhibits a similar absorption with a maximum at 543 to 544 mμ, although in some instances the absorption was shifted toward the red, the maximum varying from 546 to 553 mμ. The addition of nitrite to urines in which the N.S. test was spontaneously positive usually did not significantly alter the absorption spectra. In a few, however, the maximum intensity of the band was displaced after addition of nitrite, and in almost all such instances, the displacement was slightly toward the red end of the spectrum.

*Urinary Nitrite.* Of the 224 urines from the eight patients with nicotinic acid deficiency, the starch-iodine test was positive in 42, indicating the presence of nitrite or of a similar oxidizing agent. It is significant that in each of these 42 urines the B.E.S. and N.S. tests were also spontaneously positive. The addition of nitrite to the urine in the amount described did not influence

these tests except in one instance. In this case the B.E.S. test was unchanged but the color of the amyl alcohol in the N.S. test rapidly became yellow. This may have indicated simply an over-oxidation, since Homer [23] has reported that the color of various indol derivatives is transformed to yellow or brown in the presence of an excess of oxidizing agent. In 30 urines, the starch-iodine test was negative, but the B.E.S. and N.S. tests were spontaneously positive. It would appear that these urines contained an oxidizing agent other than nitrite, since the starch-iodine test is sensitive for smaller concentrations of nitrite than are required to give a positive urorosein reaction with pure indolacetic acid. The oxidizing substances, other than nitrite, which are present in the freshly voided urine, and which are responsible for the spontaneous B.E.S. and N.S. tests have not been identified. None of the patients had infections or other lesions in the urinary tract which might be responsible for the production of such substances.

*Urinary Indirubin-Like Substances.* The toluene preservatives of pellagra urines, also of urines from certain other patients suffering from malnutrition of one cause or another, often develop a pink or even deep red color.[1, 2] In many instances the red color is due to the formation of an indirubin-like substance.[1, 2] The present investigation has sought to determine whether the occurrence of this substance was in any way correlated with the presence of indolacetic acid, indican, the presence of an oxidizing agent in the urine, or a combination of these substances.

A pink or red color developed in the toluene in 72 of the 224 urines from the eight cases with nicotinic acid deficiency. In the remaining 152, the toluene remained clear. The B.E.S. and N.S. tests were also positive without the addition of an oxidizing agent in 72 urines but not necessarily the same samples. In 25 of these, the toluene became red; it remained clear in the other 47. In the urines in which the B.E.S. and N.S. tests were positive only after addition of nitrite, the toluene became red in 45 and remained clear in 104. The presence of nitrite or similar oxidizing substance in the urine does not, therefore, appear to be necessary to the formation of this red pigment.

When the toluene preservatives of these urines were subjected to chromatographic analysis, several pigments were found to be present. These included a red crystalline substance, closely related at least to indirubin. The general behavior of the red toluene-soluble pigments from both human and dog urine have been studied and their absorption in ultra-violet light compared with that of crystalline indirubin. These observations will be presented in a subsequent report.

In 49 of the 224 specimens of urine, the indican reaction was greater than 1 (graded on a basis of 4). In 31 of these the toluene became red; in the other 18 the toluene remained clear. There were 175 urines in which the indican reaction was less than one. In 134 of these the toluene remained clear, whereas in 41 a red pigment appeared. These observations suggest

that the formation of these red pigments occurs more frequently in those urines which contain a larger amount of indican, than in those in which the amount of indican is normal. On the other hand, a red color developed in the toluene of five urines in which the Obermayer reaction was consistently negative, as well as in several others in which the reaction was very weak. The possibility exists, however, that given the proper conditions indolacetic acid and indoxyl may unite to form indirubin. In 11 instances, we have observed that the toluene layer became red coincidentally with the disappearance of the urorosein reaction, and frequently, with a diminution in the intensity of the indican reaction. Again, however, a red color developed in the toluene in 13 urine samples in which there was no apparent change in the intensity of the urorosein reaction. Inasmuch as quantitative estimations of indolacetic acid were not made, it is quite possible that only a part was utilized in these instances in the formation of indirubin.

*Urinary Indican.* In seven of the eight patients with nicotinic acid deficiency, the amounts of indican in the urine were within normal limits prior to treatment and were not influenced by the administration of nicotinic acid. The remaining patient had a marked increase of indican in the urine, and this decreased following treatment. The decrease in urinary indican in this patient may have been due to the effect of thiamin (which was administered over the same period as the nicotinic acid) upon the size and motility of the large bowel, since considerable improvement in the function of the colon occurred following institution of therapy.

*Urinary Porphyrin.* In none of the patients with nicotinic acid deficiency whom we have studied was the amount of porphyrin in the urine sufficient to be productive of color with the Ellinger-Dojmi reaction. This fact was readily ascertained by preliminary removal of porphyrin from the ether extract of the urine with 5 per cent HCl. The urorosein reaction was then developed by extraction from the ether with 25 per cent HCl, according to the Ellinger-Dojmi procedure. In every urine so examined, preliminary removal of porphyrin with 5 per cent HCl did not interfere with the intensity of the color reaction produced by urorosein in the 25 per cent HCl. Since quantitative studies of urinary porphyrin excretion were not performed in the eight cases of nicotinic acid deficiency which we studied, the fact remains that slightly increased amounts of coproporphyrin may have been present. In the two 24 hour collections of urine from two patients suffering from endemic pellagra which were sent to us from Duke University, there were 57.8 and 75.8 micrograms of coproporphyrin, respectively. These values are within normal limits. The B.E.S. test was strongly positive in both instances. By way of comparison it may be noted that the urine from a typical case of lead colic contained 720 $\gamma$ in 24 hours, a tenfold increase, yet the B.E.S. test was negative. (The volume of urine was 1900 c.c.) Spectroscopic examination of the 25 per cent HCl from the B.E.S. test in this instance revealed weak porphyrin absorption, although the solution was prac-

tically colorless. This again reveals the complete independence of the B.E.S. test with respect to porphyrinuria. We believe that the test would not be significantly positive due to porphyrin except possibly in certain cases of idiopathic porphyria in which relatively large amounts of coproporphyrin are excreted. In most of these cases, the excess porphyrin is, of course, uroporphyrin, which is insoluble in ether, and could not, therefore, contribute to the B.E.S. test. The latter has been negative in the urines of five cases of idiopathic porphyria observed by us.

Since it has been suggested that the light sensitivity in pellagra is due to porphyrin [8] the possibility existed that there might be increased porphyrin in the feces even if not in the urine. H. van den Bergh has observed a case of idiopathic porphyria with light sensitivity, but without porphyrinuria.[41] At the suggestion of Dr. David Smith of Duke University Medical School, the stool specimens from two of his cases of endemic pellagra were studied quantitatively as described in the foregoing. The results were as follows:

1. Wt. of 4 day feces = 479 gm.

| | γ per day |
|---|---|
| Protoporphyrin | 3,280 |
| Deuteroporphyrin | 750 |
| Coproporphyrin | 400 |

2. Wt. of 4 day feces = 500 gm.

| | γ per day |
|---|---|
| Protoporphyrin | 1000 |
| Deuteroporphyrin | 1000 |
| Coproporphyrin | 242 |

The values for coproporphyrin are within normal limits, while the values for proto- and deuteroporphyrin (which are, of course, only relative) are considerably increased. This increase, however, is readily explained by the presence of occult blood in both samples (positive hemochromogen reaction).

*Results in Patients Receiving Deep Roentgen Therapy.* One hundred and seventy-three specimens of urine were examined from seven patients receiving deep roentgen therapy for squamous cell carcinoma of the cervix uteri. The results of this study are shown in table 2. A positive starch-iodine test for nitrite occurred in seven urines in which the precursor of the urorosein reaction was absent, with the result that the B.E.S. and N.S. tests were negative in these instances. This group of cases differs from the preceding in that the majority of the urines (78 per cent) failed to develop a positive urorosein reaction even after the addition of $KNO_2$. In no instance was the amount of porphyrin in the urine of these cases sufficient to be productive of color with the Ellinger-Dojmi reaction.

The occurrence of nausea, or nausea and vomiting could not be correlated either with the presence of positive B.E.S. or N.S. tests, with the amount of indican in the urine, or with the presence of an oxidizing agent in the urine. In three instances, spontaneous positive B.E.S. and N.S. tests

occurred prior to the start of the deep roentgen therapy. In one patient nausea occurred eight times during the 33 days of observation. The B.E.S. and N.S. tests were positive on only two occasions during this same period.

In 60 of these urines the toluene preservatives became pink or red when the urine was allowed to stand. In 33 of these 60 the urorosein reaction had been negative even after the addition of nitrite and there were only traces of indican present.

*Results in Patients Suffering from Arthritis.* In only one of the 38 urines examined from this group of patients was the urorosein reaction positive without the addition of nitrite. In two of the specimens there was insufficient chromogen present to give a positive test even after the addition of nitrite. As a group, the amounts of indican in these urines were not increased (see table 2), and in none did the toluene preservative become pink or red.

*Results in Patients with Diabetic Acidosis.* Eight specimens of urine were examined from five patients admitted to the hospital in severe diabetic acidosis. The urorosein reaction was not spontaneously positive in any, but was positive in seven following the addition of nitrite (table 2). A red color failed to develop in the toluene preservative of any of the eight urines.

*Results in Normal Individuals.* Thirty-four specimens of urine were obtained from 16 normal subjects and were examined immediately after voiding. The urorosein reaction was not positive spontaneously in any of these, but in 19 it became positive after the addition of nitrite (table 2). A red color failed to develop in the toluene of any of the 34 urines. Urinary indican was increased in four of the 34 samples. In none of the 34 was the starch-iodine test positive for nitrite.

## Discussion

The red pigment developing in certain urines after the addition of a strong mineral acid was named urorosein by Nencki and Sieber.[18] The chromogen of this reaction was identified by Herter as indolacetic acid.[22] Herter [24] also pointed out that the presence of an oxidizing agent in the urine was essential to the development of the reaction.

A varying incidence of positive urorosein reactions in normal and pathological urines has been reported by different investigators. Nencki and Sieber [18] noted positive tests in 10 per cent of all pathological urines, and negative tests in the urine from all normal subjects. A positive test occurred in every normal urine examined by Rosin [25] although in some the test was faint. Garrod and Hopkins [26] stated that the chromogen of urorosein is a common constituent of pathological urines, and that it is sometimes present in traces in normal urines. Herter [22] reported the urorosein reaction to be very faint in the urine of normal subjects, but that the reaction was increased following the consumption of large quantities of meat. Ross [27] found that the urines of 21 per cent of 93 healthy individuals and 43 per cent of 490

insane individuals gave a positive test following the addition of sodium nitrite. Without the aid of an oxidizing agent the tests were positive in 7.7 and 11 per cent of the cases, respectively. Gross, Sasaki, and Spies [28] report the presence of a positive (B.E.S.) test in the urine of 13 of 45 medical students. The widely divergent nature of the above reports is due probably to differences in the technic used by the various investigators (use of an oxidizing agent, amount and concentration of urine and acid, the presence of other pigments in the urine soluble in amyl alcohol which mask the color, etc.).

The development of a red color in the 25 per cent HCl in the Beckh-Ellinger-Spies test is obviously dependent upon two substances, the chromogen of urorosein, and an oxidizing agent. Since the chromogen is present in a high percentage of urines (normal as well as pathological), the chief variable in this reaction is the oxidizing agent. Herter [24] noted that nitrites were formed in many urines on standing, through the action of nitrifying bacteria. Meiklejohn and Kark [18] observed that oxidizing substances developed in urines on standing, even when kept sterile. Ross [27] obtained positive urorosein reactions in specimens of urine examined immediately after they were passed, and similar results have been obtained by Meiklejohn and Kark,[18] and by us.

Since this oxidizing agent (as yet unidentified) may occur in the freshly voided urine of normal persons, or long after all evidence of pellagra has disappeared (table 1), its presence in the urine cannot be considered as a specific test for nicotinic acid deficiency. It does appear from our studies, however, that the spontaneous urorosein reaction occurs much more frequently and in greater intensity in individuals suffering from nicotinic acid deficiency than in normal subjects.

An alteration in the mode of putrefaction of tryptophane associated with changes in the flora of the intestinal bacteria may be a contributing factor in the production of the urorosein reaction. Hopkins and Cole [29] have shown that tryptophane yields indolacetic acid when acted upon by anaerobic bacteria, whereas under aerobic conditions of growth, skatolcarbonic acid, skatol, and indol are formed. This difference in the metabolism of tryptophane may account, at least in part, for the observations that a reciprocal ratio exists between the output of indican and of urorosein in the urine, and that this ratio may be influenced by diet.[14, 25, 30] Decarboxylation of the amino acids may be effected by a large number of organisms, especially anaerobic bacilli. The action of such bacteria on tryptophane, therefore, may lead to the production of indolethylamine. When this substance was perfused through the surviving liver of the rabbit or cat, Ewins and Laidlow [31] found the perfusion fluid gave a strong urorosein reaction, and that indolacetic acid could be isolated from this fluid. It has not been demonstrated that an altered tryptophane metabolism is responsible for the urorosein reaction in human urine, but since many of the conditions in which a

strong urorosein reaction have been reported are accompanied by some degree of intestinal disorder, this point requires further study.

Increased urinary excretion of coproporphyrin has been observed in alcoholic pellagra by Dobriner, Strain, and Localio,[32] and by Watson.[1] Following treatment with yeast and nicotinic acid, a significant decrease in the amounts occurred. Rosenblum and Jolliffe [33] reported an increased urinary excretion of porphyrin in six of nine inebriates who had either a pellagrous stomatitis, dermatitis, or both. In three of the subjects there appeared to be a definite correlation between the severity of the pellagra and porphyrin excretion. More recently, Kark and Meiklejohn [44] have reported no increase of urinary porphyrin in six of seven cases of pellagra; a slight increase was observed in one instance of alcoholic pellagra. No correlation exists between the B.E.S. test and the actual amounts of urinary porphyrin, as shown by Watson,[1] and Dobriner and Rhoads.[12] Furthermore, in none of the patients suffering from nicotinic acid deficiency whom we have studied was the amount of porphyrin in the urine sufficient to be productive of color in the Ellinger-Dojmi reaction. The amounts of porphyrin present in the urine in alcoholic pellagra are not as great as are often encountered in lead poisoning, cirrhosis of the liver, or other pathological states. There is, therefore, no reason to suppose, as has been suggested, that the light sensitivity in pellagra is related to porphyrin. The amounts in the urine and feces of the two cases of endemic pellagra of the present study were normal.

An increased excretion of coproporphyrin in the feces has been noted in one case of pellagra associated with chronic alcoholism by Dobriner, Strain and Localio.[32] An average of 643 micrograms of coproporphyrin was excreted daily in the feces by this patient during a six-day control period. Following nine days of treatment with yeast extract and the intramuscular injection of liver extract, the fecal excretion of coproporphyrin decreased to less than half of the original level. Large amounts of protoporphyrin and deuteroporphyrin were also found in the feces of this patient, but these may well have been the result of bleeding into the gastrointestinal tract, as these authors have suggested. It may be noted that blood loss alone is sufficient to increase erythropoiesis and with this, the amount of coproporphyrin in the feces.[34]

The B.E.S. test has also been used as a measure of porphyrin excretion in roentgen sickness. Spies, Bean, and Stone [35] reported "abnormally large" amounts of porphyrin in the urine of seven cases of radiation sickness, and stated that these levels returned to normal following the administration of nicotinic acid. Graham [15] reported that 10 of 52 patients suffering from radiation sickness "showed a material increase in porphyrinuria," using the method of Beckh, Ellinger, and Spies.[4] He stated that all but one of these returned to normal after the administration of nicotinic acid, and that "even when the excretion of porphyrin appeared to be within normal limits in most cases, it was decreased when nicotinic acid was given."

In none of seven patients receiving deep roentgen therapy in our series was the amount of porphyrin present in the urine sufficient to be productive of color when extracted from the ether extract (in the B.E.S. procedure) with 5 per cent HCl. We were unable to establish any correlation between a positive B.E.S. test and the occurrence of nausea in these patients. Furthermore, in every instance the B.E.S. test became negative within one or two days without the administration of nicotinic acid.

Lutterloh [16] has reported the B.E.S. test to be positive in 14 of a group of 49 patients suffering from atrophic arthritis. In our study of 38 unselected arthritics having no clinical evidence of nicotinic acid deficiency, we found only one positive B.E.S. test (in a patient with hypertrophic arthritis).

Vilter, Vilter, and Spies [17] noted the B.E.S. test to be positive in one of two cases of severe diabetic acidosis, and reported that this test became negative following treatment of the acidosis. In five cases which we have observed, we have found the test to be negative. Although codehydrogenase I was believed by these investigators to be deficient in the blood of pellagrins in relapse as well as in the blood of diabetics in severe acidosis, there is insufficient evidence that lack of this substance is responsible for the conditions which lead to the production of a positive B.E.S. test.

A strongly positive indican reaction has been described in the urine of patients suffering from endemic pellagra,[14, 36, 37, 38] and it has been noted frequently that the indicanuria decreases as the patient recovers. On the other hand, the production of pellagra in 11 human volunteers by Goldberger and Wheeler [39] was not accompanied by marked indicanuria. In these 11 subjects the indican reaction of the urine was recorded as negative more often than positive. The incidence of indicanuria appears to be greater among cases with a deficiency of gastric acid,[14, 40] and it has been suggested that the diminished gastric acidity is indicative of the strong inhibitory influence of the normally acid gastric juice upon gastrointestinal putrefaction. In only one of our eight cases was the amount of indican in the urine significantly increased. Since both thiamin and nicotinic acid were administered simultaneously to this patient, it is not possible to state with certainty that nicotinic acid was responsible for the decreasing indicanuria which accompanied his clinical improvement. In the remaining seven patients the amounts of indican in the urine were within normal limits prior to treatment, and were not significantly altered by the administration of nicotinic acid.

Since completion of the studies described above, Najjar and Holt [42] have described a specific urinary reaction which is apparently dependent upon the store of nicotinic acid in the body. The substance responsible for this reaction has not been identified, but the bluish fluorescence which it produces in ultraviolet light may be measured quantitatively. After the ingestion of nicotinic acid the excretion of this substance increased. It was demonstrated that the substance responsible for the fluorescence disappears from

the urine of patients with pellagra and of dogs with blacktongue.[48] A second unknown substance which produces fluorescence in the "blank," has been observed to be increased in pellagra.

When an aqueous solution of indolacetic acid, or of indolacetic acid plus a few drops of 2 per cent $KNO_2$, was used in this test, no increased fluorescence occurred. After shaking with permutit, the solution of indolacetic acid was decanted and tested for the urorosein reaction. The urorosein reaction which resulted was as intense as occurred with a similar control solution, indicating that neither indolacetic acid nor an intermediate compound in the urorosein reaction was adsorbed on the permutit. It appears from these observations, therefore, that no direct relationship exists between the substances which are responsible for the fluorescence reaction of Najjar and Holt and the urorosein test in pellagra.

## Conclusions

1. The chromogen of the urorosein reaction is a normal constituent of the urine of many individuals who have no clinical evidence of nicotinic acid deficiency. The available evidence indicates that this chromogen is indolacetic acid.

2. The development of the urorosein reaction either by the method of Nencki and Sieber, or that of Beckh, Ellinger and Spies, requires the presence of nitrite or a similar oxidizing agent. Substances of this type are native to urines which exhibit spontaneous reactions. The exact nature of these native substances remains to be determined.

3. No definite correlation has been noted between the presence and disappearance of either chromogen or oxidizing agent, with the deficiency or administration respectively, of nicotinic acid. The results of the present investigation indicate, however, that spontaneous reactions (without addition of nitrite) occur only in association with disease and much more frequently in subjects having deficiency states.

4. The Ellinger-Dojmi color reaction, on which the B.E.S. test is based, is not at all specific for porphyrin, and in our experience has always been due to urorosein.

5. The development of a red color in the toluene preservatives of pellagra urines, also of urines from certain patients with malnutrition of one cause or another, could not be correlated with other evidence of nicotinic acid deficiency. This pigment has not been observed to develop in urines of normal individuals.

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# STUDIES OF URINARY PIGMENTS IN PELLAGRA AND OTHER PATHOLOGICAL STATES. II. THE EXCRETION OF PORPHYRIN AND THE UROROSEIN REACTION IN DOGS WITH EXPERIMENTAL BLACKTONGUE *

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IN the preceding paper [1] and in previous communications [2, 3] it has been shown that the Beckh-Ellinger-Spies (B.E.S.) test [4] is due to urorosein and that positive reactions are correlated in all instances with positive Nencki-Sieber (N.S.) tests for urorosein. Distinct increases of coproporphyrin were noted in alcoholic,[2] but not in endemic pellagra.[1, 3] Even in the former, the amounts of porphyrin were insufficient to be productive of color in the B.E.S. test. In order to study the effect of nicotinic acid in the absence of complicating factors such as alcoholism or other coexisting disease, the following studies were carried out in dogs with blacktongue.

## METHOD

Blacktongue was produced in female mongrel dogs, using the Goldberger diet No. 123.[5] The dogs were kept in metabolism cages to facilitate the collection of urine, but were allowed outside for exercise once daily. Precautions were taken in the care and cleaning of the cages to guard against contamination of the urine by feces insofar as this was possible. The urines were collected in 24 hour periods for the porphyrin determinations; petroleum ether was added to the collection bottles at the start of each period, as a preservative. When determinations for the other urinary pigments were carried out, toluene was used as the preservative, and the urines were usually examined within a few hours of passage in order to prevent changes due to bacterial growth.

The animals were observed for control periods of 16 to 20 days before the start of the blacktongue-producing diet. They were then maintained on this diet until they had developed a marked stomatitis, and had refused food for several days. Every animal exhibited evidence of blacktongue for at least one week before treatment was instituted. In all but one of the dogs, therapy consisted of the intramuscular administration of from 250 to 600 milligrams of nicotinic acid † and the replacement of the Goldberger diet by

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† The nicotinic acid was supplied in a sterile solution combined with monoethanolamine ("Nicamin") through the courtesy of Abbott Laboratories, North Chicago, Illinois.

the standard laboratory diet. In the remaining animal, the blacktongue-producing diet was continued, but a temporary regression of the oral lesions of the disease was produced by feeding three-fourths of a pound of fresh beefsteak after a severe attack of blacktongue had been produced. With the exception of one dog which died on the fifth day following treatment, the animals were observed for periods of not less than two weeks after treatment.

Coproporphyrin was determined by the modification of the Fikentscher method as described in paper I.[1] The Beckh-Ellinger-Spies test and the Nencki-Sieber test were performed in the same manner as described previously.[1] Toluene was added to 45 specimens of urine from three dogs with experimental blacktongue. The samples were collected at various stages of the disease and were allowed to stand in the light for periods of not less than three weeks. Twenty specimens of urine from three normal dogs were treated in a similar manner.

## Results

*Porphyrin Determinations.* Three dogs were used in this experiment. The daily excretion of porphyrin in the urine of these animals while on the standard laboratory diet during the control period varied from 27.6 to 81.3 micrograms of coproporphyrin for a 48 hour period of collection. With exception of dog number 1, in which there was a questionable rise, no significant change occurred in the daily excretion during the period of induction, the acute phase of the disease, or during the period of regression of the disease (table 1).

*B.E.S. and N.S. Tests.* In the normal dog, these tests were always negative if the urine was examined within a few hours of passage. If a few drops of 2 per cent solution of potassium nitrite were added to 10 or 20 c.c. of urine and the tests repeated, a reddish-purple color developed in the 25 per cent HCl in the B.E.S. test, or in the amyl alcohol in the N.S. test. If the urine was allowed to stand uncovered in the laboratory without a preservative for 24 hours or longer, frequently the B.E.S. and N.S. tests were positive without the addition of nitrite.

The pigment responsible for this color reaction in the urine of the dog has not been identified. A similar color reaction occurred in the urines from five of six normal dogs. This pigment differs from urorosein in that it has a more purplish color in 25 per cent HCl and in amyl alcohol, and that the spectroscopic absorption is much fainter in proportion to the color intensity of the solution. When a few drops of 2 per cent solution of potassium nitrite are added to dog urine and the B.E.S. test performed, extraction of the ether with a few cubic centimeters of 25 per cent HCl is followed by the production of a red-purple color. When examined spectroscopically, this acid solution exhibits a broad diffuse absorption band with maximum intensity at about 539–540 mμ. The edges of this band are poorly defined,

TABLE I

Urinary Excretion of Coproporphyrin, Expressed as Micrograms per Two Day Period of Collection, in Dogs Receiving a Blacktongue-Producing Diet

| Number of days observed | Dog no. 1 | | | Dog no. 2 | | | Dog no. 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Micrograms of copro-porphyrin | Weight in kilos | Remarks | Micrograms of copro-porphyrin | Weight in kilos | Remarks | Micrograms of copro-porphyrin | Weight in kilos | Remarks |
| | Control period | | | Control period | | | Control period | | |
| 1– 2 | 50.3 | 18.4 | Normal dog | 27.6 | 14.1 | Normal dog | 70.4 | 11.8 | Normal dog |
| 3– 4 | 63.2 | | | | | | | | |
| 5– 6 | 49.2 | | | 32.6 | | | 53.3 | | |
| 7– 8 | 81.3 | | | | | | | | |
| 9–10 | 61.2 | | | 52.1 | | | 48.9 | | |
| 11–12 | 70.0 | | | | | | | | |
| 13–14 | 42.1 | | | 38.9 | | | 57.6 | | |
| 15–16 | 53.2 | | | | | | | | |
| 17–18 | 61.7 | | | | | | 68.3 | 12.1 | |
| 19–20 | 57.8 | 18.4 | | | | | | | |
| | Blacktongue-producing diet started | | | Blacktongue-producing diet started | | | Blacktongue-producing diet started | | |
| 1– 2 | 52.2 | | | 48.7 | 13.9 | | 59.9 | | |
| 3– 4 | 49.1 | | | | | | | | |
| 5– 6 | 31.4 | | | 63.8 | | | 43.8 | | |
| 7– 8 | 29.4 | | | | | | | | |
| 9–10 | 69.2 | | | 28.6 | | | 56.9 | | |
| 11–12 | 56.3 | | | | | | | | |
| 13–14 | 39.6 | | | 29.4 | | | 93.8 | | |
| 15–16 | 41.0 | 19.1 | | | | | | | |
| 17–18 | 50.6 | | | | | | 46.8 | | |
| 19–20 | 67.2 | | | 47.6 | | | | | |
| 21–22 | 73.0 | | | | | | 57.1 | 10.9 | |
| 23–24 | 43.1 | | | 38.3 | | | | | |
| 25–26 | 60.3 | | | | | | 50.4 | | |
| 27–28 | 69.2 | | | 50.4 | | | | | |
| 29–30 | 88.6 | | | | | | 63.6 | | |
| 31–32 | 80.0 | | | 22.3 | | | | | |
| 33–34 | 73.3 | | | | | | 74.6 | 10.2 | Mouth normal |
| 35–36 | 88.1 | 19.8 | Mouth normal | 43.3 | 14.1 | Mouth normal | | | |
| 37–38 | 60.3 | | | | | | 64.7 | | Mild inflammation of the buccal mucosa |
| 39–40 | 71.4 | | | 18.8 | | | | | |
| 41–42 | 89.3 | | | | | | 53.7 | 10.2 | |
| 43–44 | 100.2 | | | 38.7 | | | | | |
| 45–46 | 73.8 | | | | | | 70.4 | | |
| 47–48 | 88.8 | | | 43.8 | | | | | |
| 49–50 | 54.1 | | | | | | 63.6 | | |
| 51–52 | 89.3 | 19.5 | Mild inflammation of the buccal mucosa | 39.3 | | | | | |

TABLE I (*Continued*)

| | Dog no. 1 | | | Dog no. 2 | | | Dog no. 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

TABLE I (*Continued*)

| Number of days observed | Dog no. 1 | | | Dog no. 2 | | | Dog no. 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Micrograms of copro-porphyrin | Weight in kilos | Remarks | Micrograms of copro-porphyrin | Weight in kilos | Remarks | Micrograms of copro-porphyrin | Weight in kilos | Remarks |
| 53–54 | 96.2 | | | | | | 74.8 | 10.2 | Severe blacktongue was present. Animal was very ill. Three-fourths of a pound of fresh beef steak was given to the dog; the Goldberger diet was continued |
| 55–56 | 63.8 | | | 48.8 | 13.6 | Mild inflammation of the buccal mucosa | | | |
| 57–58 | 60.2 | | | | | | | | |
| 59–60 | 88.7 | | | 58.3 | | | | | |
| 61–62 | 66.3 | 18.4 | Stomatitis has become quite severe | | | | | | |
| 63–64 | 93.1 | | | 47.9 | | | | | |
| 65–66 | 79.9 | | | | | | | | |
| 67–68 | 63.8 | | | 38.3 | | | | | |
| 69–70 | 77.1 | 17.3 | Severe blacktongue was present. Goldberger diet was discontinued and normal diet resumed | 48.3 | | | | | |
| 71–72 | | | | 51.2 | | | | | |
| 73–74 | | | | 46.3 | 13.0 | Severe blacktongue was present. Goldberger diet was discontinued and normal diet resumed | | | |
| | Period of regression of the blacktongue lesions | | | Period of regression of the blacktongue lesions | | | Period of regression of the blacktongue lesions | | |
| 1– 2 | 39.7 | | | 50.6 | | | 59.2 | | |
| 3– 4 | * | | | 33.8 | | 250 mg. of nicotinic acid were given during the first four days of treatment | | | Improvement of the stomatitis |
| 5– 6 | | | | 46.9 | | | 83.7 | 9.8 | |
| 7– 8 | | | | 60.3 | | | | | |
| 9–10 | | | | 38.8 | 13.9 | All lesions of black-tongue had disappeared | 76.3 | | |
| 11–12 | | | | 30.3 | | | | | |
| 13–14 | | | | 50.8 | | | 68.4 | | |
| 15–16 | | | | 38.8 | | | | | |
| 17–18 | | | | 46.3 | 13.9 | Dog normal. No evidence of blacktongue | 57.5 | 9.5 | Inflammation of the mouth has subsided; the meat produced only a temporary remission of the disease, however |

* This animal received 600 milligrams of nicotinic acid intramuscularly during the first four days of treatment, and the inflammation of the mouth had begun to subside. The dog died suddenly, however, about 100 hours after the start of therapy; the cause of death was undetermined. Urine collection during the last two day period was incomplete.

but have been measured at 532 to 556 mμ. The pigment is not extracted from ether with 5 per cent HCl, and only to a slight extent with 10 per cent HCl.

This red pigment can be extracted readily with amyl alcohol from the dog's urine following treatment with nitrite and 25 per cent HCl. In amyl alcohol a faint, diffuse absorption band is noted with maximum intensity at 539 mμ. The presence of other pigments, however, such as indican and urobilin, frequently masks the red color in the amyl alcohol.

The metabolism of tryptophane is different in the dog from in man in that kynurenic acid is a normal constituent of the urine of the former, whereas it is doubtful if this substance is formed in man. It occurred to us, therefore, to determine whether kynurenic acid might be responsible for the above-mentioned color reaction in the dog's urine. However, aqueous solutions of kynurenic acid * to which $KNO_2$ had been added failed to exhibit any color in either the B.E.S. or N.S. tests.

The B.E.S. and N.S. tests were carried out on the urines of three dogs during the stage of induction of blacktongue, in the acute phase as well as during a control period before and after the period of feeding the Goldberger diet. Both tests were negative throughout. Spies and his associates[6, 7] have likewise noted that the urine from dogs with spontaneous blacktongue does not give a positive B.E.S. test.

The toluene preservative remained clear in 39 of the urines from the three dogs with blacktongue. In the remaining six, a red color developed in the preservative. No correlation could be established between the severity of the disease at the time the urine was collected and the appearance of the red pigment in the toluene. The feeding of three-fourths of a pound of fresh beefsteak to one dog was not associated with the development of a red color in the toluene. In 12 of the urines from the normal dogs, the toluene remained clear, whereas a red color developed in the remaining eight. It appears from these observations, therefore, that the development of a red color in the toluene preservatives of dog urines is not correlated with nicotinic acid deficiency. The characteristics of two red pigments which were present in the toluene will be described in a separate communication.

## Conclusions

1. The spontaneous urorosein reaction was consistently negative in urine samples from dogs having experimental blacktongue.

2. The appearance of red color in the toluene preservatives of dog urines was not correlated in any way with nicotinic acid deficiency.

3. There was no significant increase in coproporphyrin excretion in dogs with blacktongue over that observed during the control periods.

* Samples of kynurenic acid were obtained through the courtesy of Hoffmann-La Roche, Nutley, New Jersey, and Dr. Clarence P. Berg, State University of Iowa, Iowa City, Iowa.

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# STUDIES OF URINARY PIGMENTS IN PELLAGRA AND OTHER PATHOLOGICAL STATES. III. CERTAIN TOLUENE SOLUBLE PIGMENTS OF HUMAN AND CANINE URINE *

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Toluene preservatives of urine from pellagrins and from certain other patients suffering from malnutrition of one cause or another have been observed in many instances to develop a pink or deep red color upon standing.[1, 2, 3] The development of this red pigment appears not to depend upon the presence of nicotinic acid deficiency, since it was observed in the preservatives of urines from patients who did not have any evidence of this deficiency.[3] No change was seen in the toluene preservatives of 72 urines from 54 individuals who were normal, or who had arthritis, but no evidence of other disease. In an earlier investigation, Watson [2] had noted that the characteristics of the red pigment extracted by the toluene corresponded closely with those of indirubin or indigo red. Since further study showed that often more than one red pigment was extracted by the toluene, it seemed advisable to investigate these substances in more detail.

## Method and Materials

*Human Urine.* Ten cubic centimeters of toluene were added to about 150 c.c. of urine, which was allowed to stand in the light for a period of at least three weeks and observed for the development of a red color in the toluene layer. The urines were obtained from a number of patients who had clinical evidence of nicotinic acid deficiency, from seven patients who had squamous cell carcinoma of the cervix uteri, and who were receiving deep roentgen therapy, as well as from a number of patients who were in the hospital because of one condition or another (see paper I). All of the toluene preservatives which became pink or red were pooled and were concentrated in vacuo to a small volume. The pigments were taken up in a small amount of ethyl acetate, to which was added 20 parts of petroleum ether. This solution was passed through a column of Brockmann's $Al_2O_3$ † according to the usual method of preparing a flowing chromatogram. A number of different pigments were separated in this manner (figure 1). By means of elution with increasing concentrations of ethyl acetate in petroleum

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ether, the two red pigments (6 and 7 in figure 1) were isolated. They were purified further by passage through a new column of $Al_2O_3$, and were recrystallized out of hot ethyl acetate.

*Canine Urine.* Toluene was added to 45 specimens of urine from three dogs in which experimental blacktongue had been produced by the feeding of Goldberger diet No. 123 (as described in paper II). The samples of urine were collected at various stages of the disease and were allowed to stand in the light for periods of not less than three weeks. In 39 specimens

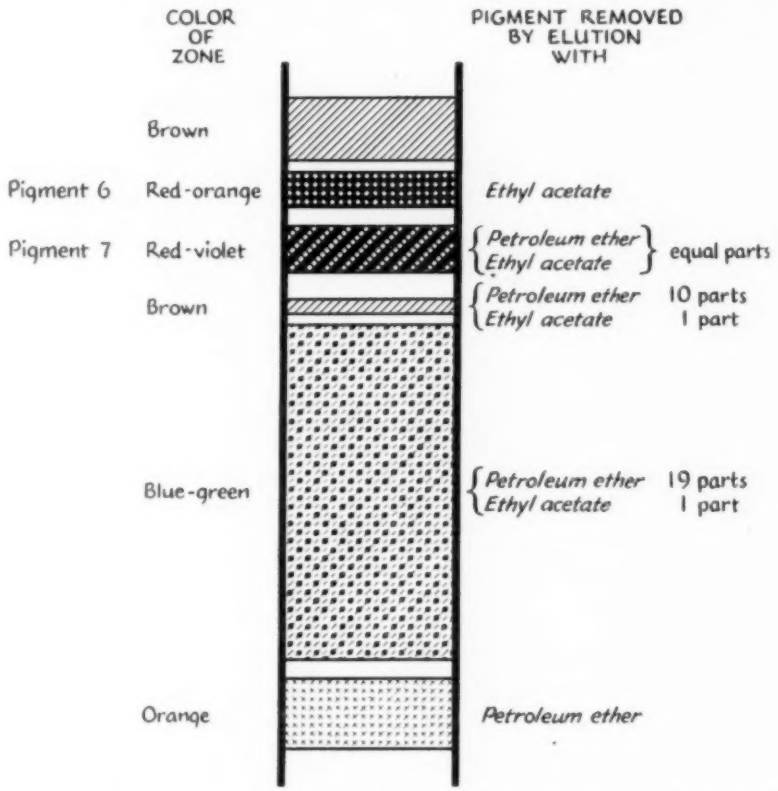


FIG. 1. Chromatographic separation of toluene soluble pigments from human urine.

the toluene remained clear; in the remaining six a red color developed in the preservative. As stated in paper II, no correlation was apparent between the severity of the disease at the time the urine was collected and the development of the red pigment. The toluene preservatives of eight from a group of 20 specimens of urine from three normal dogs developed a similar red color.

The red toluene preservatives from the 14 specimens of urine were combined and were concentrated in vacuo to less than five cubic centimeters. The residue was dissolved in 15 c.c. of ethyl acetate and was made up to 400

c.c. with petroleum ether. This solution was passed through a column of $Al_2O_3$ in the usual manner. The red and violet pigments (4 and 5 in figure 2) were purified by passage through a new column of $Al_2O_3$ and by repeated crystallization.

*Synthetic Indirubin.* A small quantity of indirubin* which had been synthesized from isatin and indoxyl, was dissolved in ethyl acetate, to which was added nine parts of petroleum ether, and this solution was passed through

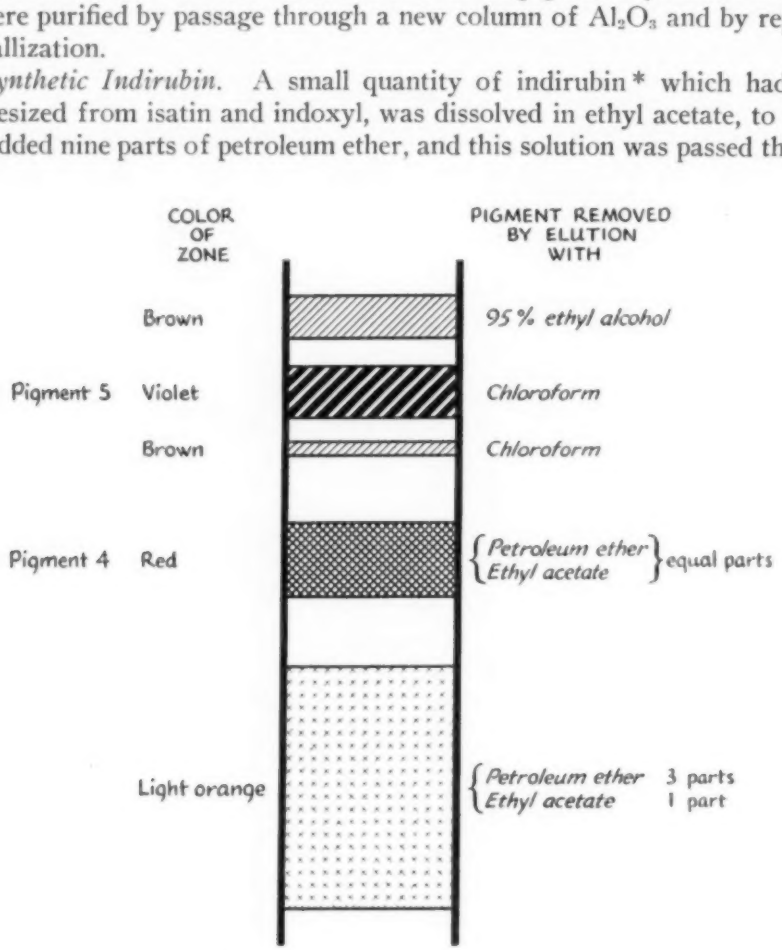


FIG. 2. Chromatographic separation of toluene soluble pigments from canine urine.

a column of $Al_2O_3$. All of the pigment was adsorbed on the top of the column, however, and elution with increasing concentrations of ethyl acetate in petroleum ether, up to equal parts of the two solvents, resulted in little change in their position. Elution with chloroform resulted in the chromatogram represented in diagrammatic form in figure 3.

Studies of the absorption of the pigments in the ultraviolet region of the spectrum were carried out by the photographic method with a Hilger quartz prism spectrograph and a Judd-Lewis spectrophotometer. The synthetic

* The indirubin used in this study was obtained through the courtesy of Dr. E. K. Bolton, Chemical Director, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

indirubin was dissolved in absolute ethyl alcohol in a concentration of 1.175 milligrams per 100 c.c. ($4.5 \times 10^{-5}$ moles per liter).

The concentration of the natural red or violet pigments, as isolated from urine, was adjusted to approximately the same absorption at the maximum near 290 mμ. Cells of 1.0 and 0.2 centimeter length were used with each solution. The scale is the logarithm of the molecular extinction coefficient for synthetic indirubin (prior to chromatographic analysis) (pigment 1, figure 4). The curves for the other solutions were shifted so that the values at the maximum near 290 mμ exactly matched that for indirubin. All

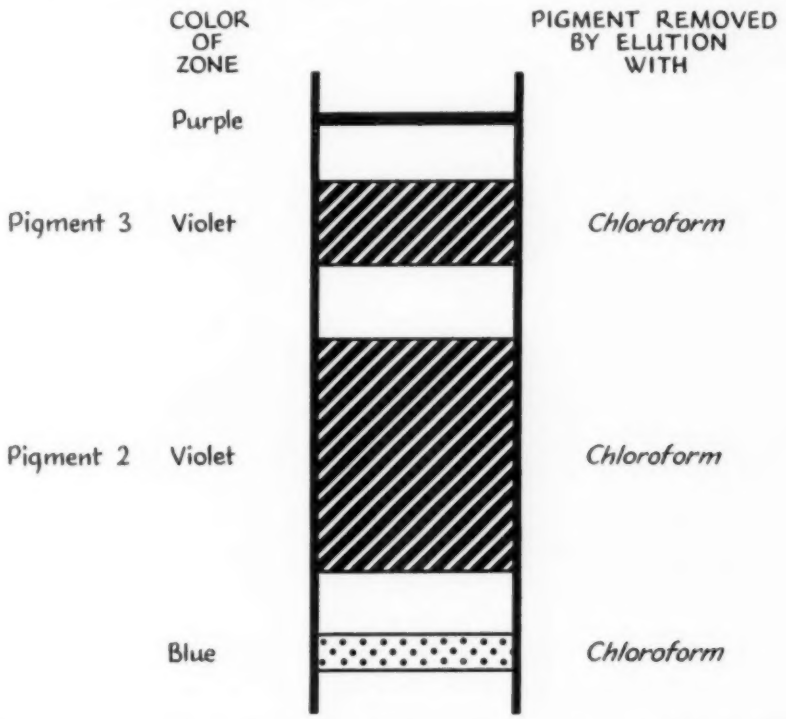


FIG. 3. Chromatographic separation of components of crude synthetic indirubin.

measurements were made with freshly prepared solutions, since solutions of pigments VI and VII were observed to be unstable. The spectrum of pigment VII (taken after several weeks) showed a broad absorption band between 410 mμ and 450 mμ which was not present in the spectrum of the freshly-prepared solution.

Sublimation temperatures were observed in the following manner: crystals of the sample being studied were placed on a round cover slip as usually employed for micro-melting point determinations with the Fisher-Johns apparatus.* After placing the cover slip in the well of the apparatus, it is

* Fisher Scientific Company, Pittsburgh, Pa.

covered with a glass slide which bridges the well, leaving an air space of about 2 mm. between cover slip and slide. As the temperature rises, it is now possible to note the beginning of sublimation by means of focusing on the under surface of the glass slide and observing the first appearance of crystals there. It is believed that this affords a much sharper method of comparing sublimation temperatures than hitherto available.

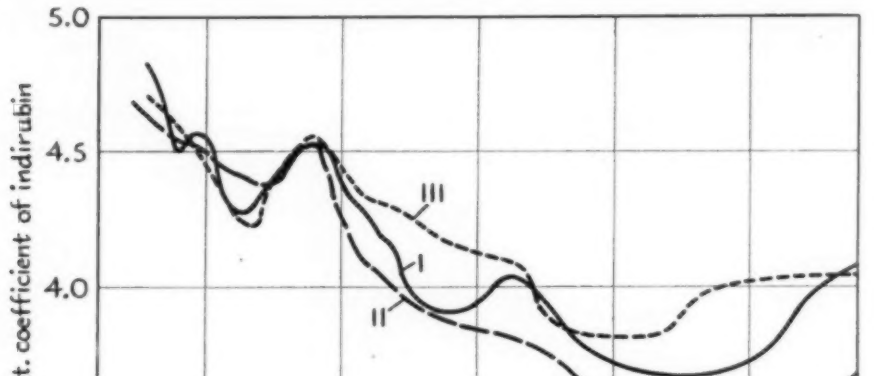


FIG. 4. Ultraviolet spectral distribution curves of crude synthetic indirubin and component substances as separated by chromatographic analysis.

## OBSERVATIONS

Six pigments were present in the toluene extract of the human urines, as demonstrated by their behavior on the column of $Al_2O_3$ (figure 1), and five pigments were separated from the toluene extracts of canine urine (figure 2). The absorption in the ultraviolet region of the four red or violet pigments is shown in figure 5. Pigment 4 (dog urine) and pigment 7 (human urine) had a similar, although not identical absorption in the ultraviolet region and behaved in a similar manner on the $Al_2O_3$ column. The absorption of the other colored pigments was not studied.

Two distinct violet pigments were separated by the passage of the synthetically prepared indirubin through the $Al_2O_3$ column. The absorption of these two pigments in the ultraviolet region differed from one another and from the absorption of the "whole" indirubin (figure 4). The absorption of the latter agrees closely with that reported previously by Cholewinski and Marchlewski.[4]

The following sublimation temperatures were observed:

| Crystals | Temperature at which sublimation was first noted (first crystals appeared on slide) | Comment |
|---|---|---|
| 1. Crude indirubin (before chromatographic analysis) | 188° C. | Large, curving and branching needles at first. Rosettes of straight needles at 250° C. |
| 2. Pigment 3 (from synthetic indirubin), figure 3 | 172° C. | Crystals had disappeared from cover slip above 235° C. |
| 3. Pigment 7 (from human urine), figure 1 | 153° C. | Crystals had disappeared from cover slip above 225° C. |

When dissolved in absolute alcohol all of the seven red or violet pigments exhibited a light blue fluorescence in ultraviolet light. Solutions of pigments

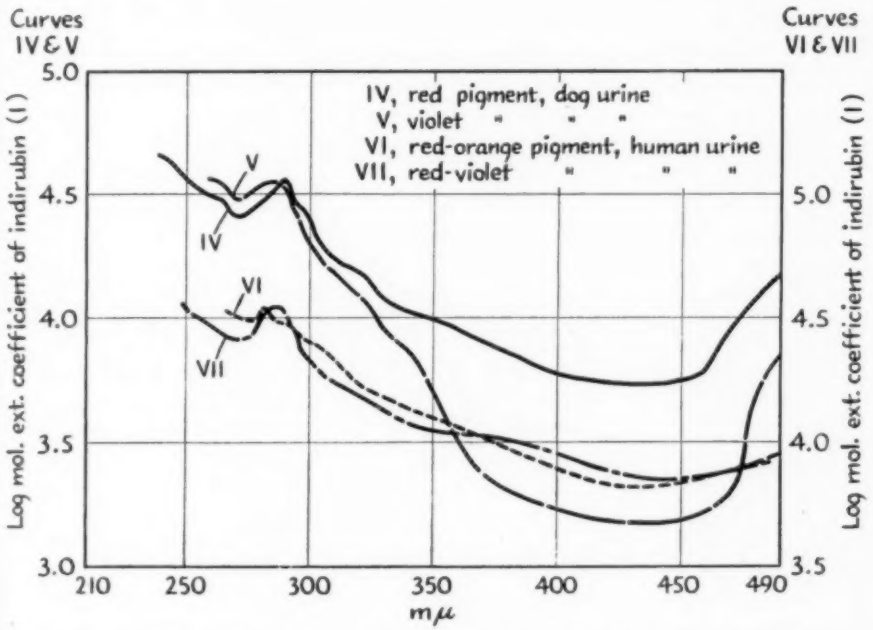


FIG. 5. Ultraviolet spectral distribution curves of the red and violet toluene soluble pigments from human and canine urines.

VI and VII which had stood in the light for over a month gave a green or bluish green fluorescence when reëxamined. The fluorescence of the other pigments did not change on standing.

## DISCUSSION

It is evident from the results just given that none of the red or violet pigments isolated from the toluene extracts of either human or canine urines was identical with synthetic indirubin. Chromatographic analysis, ultraviolet spectral distribution curves, and sublimation temperatures of the latter substance revealed clearly that neither the crude indirubin nor its component

pigments were identical with the human or canine pigments. At the same time, it appears that they are all closely related substances. For the time being it can only be stated that the natural pigments are indirubin-like in character.

## Summary and Conclusions

1. The red pigment extracted by toluene from certain human and canine urines (papers II and III) has been shown by means of chromatographic analysis to be composed of several similar pigments.

2. Two pigments each from human and canine urines were found very similar to, but not identical with, synthetic indirubin. On the basis of chromatographic analysis and spectral distribution curves, the latter was likewise shown to be a mixture of related pigments, none of which was entirely identical with any of those from the urine.

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# DUPUYTREN'S CONTRACTURE AS A SEQUEL TO CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION *

By KENNETH C. KEHL, M.D., F.A.C.P., *Racine, Wisconsin*

REPORTS of Dupuytren's contracture in association with disease of the coronary arteries have been infrequent. Askey,[1] in reviewing the syndrome of painful disability of the shoulder and hand following coronary occlusion, suggested the possible relationship of changes in the palmar aponeurosis and myocardial infarction. To the seven cases described by him are added the six cases here presented, and points of difference and similarity are noted.

## CASE REPORTS

*Case 1.* P. H., a 48 year old white male, a laborer, in April 1936, complained that since 1931 he had noted abdominal distention, belching, flatulence, and cramping lower abdominal pain which had recurred at irregular intervals. These symptoms were aggravated by taking high roughage foods, especially during periods of mental or emotional stress. At this time there were no symptoms considered to be referable to the heart.

The family history was irrelevant. At the age of 18 years he had had migratory joint pains involving both the upper and lower extremities, associated with fever and requiring bed rest. He had had pneumonia in infancy and again at the age of 16 years.

Examination when he was first seen revealed slight tenderness over the cecum and sigmoid and moderate gaseous distention. A soft, systolic apical murmur was present without demonstrable cardiac enlargement. There was no evidence of cardiac decompensation. In view of the rheumatic history the cardiac findings were thought possibly to indicate a rheumatic mitral lesion.

He was not seen again until May 12, 1939, when he was admitted to the hospital in acute left ventricular failure. For about one year prior to that time he had noted dyspnea of mild degree on exertion, cough, excessive fatigue, nocturia and nervousness, but he had been able to continue at his rather heavy work.

On examination the heart was definitely enlarged to the left with a regular rhythm and a rate of 80 per minute. A loud, rough, systolic aortic murmur was heard followed by a faint aortic second sound. There was also a rough murmur at the apex obscuring the first sound. The blood pressure was 132 mm. Hg systolic and 80 mm. diastolic. Occasional moist râles were found in both bases. No enlargement of the liver was noted and there was no peripheral edema.

During the week following his admission to the hospital there was at no time any elevation of temperature or leukocytosis.

An electrocardiogram taken on May 23, 1939, showed slight slurring of the QRS complexes in all the standard leads. $ST_1$ was isoelectric and $T_1$ of very low voltage. $ST_2$ and $ST_3$ were coved and depressed. $T_2$ and $T_3$ were inverted. Left axis deviation was present. Lead IV showed no significant deviation from normal. The impression was myocardial infarction, posterior type.

He improved on bed rest, sedation, and aminophyllin and his convalescence was uneventful until July 10, 1939, when he again experienced nocturnal paroxysmal

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dyspnea. At this time he noted the onset of the aching pain in the left clavicle and left shoulder. Shortly following his discharge from the hospital on August 12, 1939, a thickened area in the palmar fascia of the right hand at the base of the little and ring fingers, resembling an early Dupuytren's contracture, was discovered. The thickening in the palmar fascia of the right subsequently progressed to a typical Dupuytren's contracture of marked degree. About four months later changes were noted in the left palm and since then they progressed until the contracture was about equal bilaterally. During the period over which the contractures were developing he suffered from a more or less constant aching pain in both shoulders. Motion at the shoulder, especially abduction and external rotation, was limited and painful in both arms and there was tenderness to pressure over the shoulder joints and lateral aspects of the arms. At the time of the development of the Dupuytren's contracture there was aching in the hands but no redness or swelling was noted. Numbness, tingling and coldness of the hands also were complained of at that time.

Following his discharge from the hospital he had frequent episodes of acute left ventricular failure and he had been a cardiac invalid since May 1939. The shoulder disability remained such that he required assistance in dressing and undressing.

He was reëxamined in June 1941, slightly more than two years after coronary occlusion, with the following findings: The fingers of both hands were livid and cold to the touch. A marked arcus senilis was present and the ocular fundi showed thickened and tortuous arteries. Temporal arteries were prominent, tortuous and definitely thickened. A nodular enlargement of the thyroid was palpable. Moist râles were heard in the right lung base posteriorly and laterally. The heart was enlarged to the left and downward. The apex impulse was barely perceptible but well localized. The cardiac rhythm was regular except for very rare premature contractions. The rate was 72 per minute. The first sound at the apex was replaced by a blowing murmur. Along the left of the sternum a rough systolic murmur was heard which was of maximum intensity at the aortic area. This murmur was transmitted into the neck. The second aortic sound could not be heard. The blood pressure was 144 mm. Hg systolic and 86 mm. diastolic. There was no enlargement of the liver or evidence of peripheral edema. Kahn test was negative. Blood and urinary findings were not exceptional. The basal metabolic rate was within normal limits.

Both hands showed the classical picture of Dupuytren's contracture of an advanced degree (figure 1). The skin of the palms was thrown into deep folds and ridges, thickened and firmly adherent to the underlying aponeuroses. Although flexion was only slightly impaired, it was impossible to extend completely the ring or little fingers of either hand. The shoulders remained painful and tender, and motion continued to be limited.

An electrocardiogram taken on June 9, 1941, showed the following: Slurring of the QRS complexes persisted in the standard leads. $T_1$ remained upright with the voltage slightly increased. $T_2$ had become diphasic. $ST_3$ remained slightly coved and $T_3$ was inverted to a lesser degree. Left axis deviation was more marked with decreased $R_3$ and increased $S_3$ voltage. Lead IV remained practically unchanged.

In January 1942 the contractures in the palms had progressed until all fingers of both hands were involved.

*Case 2.* T. B., a 40 year old white male, an advertising executive, was seen for the first time on May 10, 1939. On the previous evening, following a heavy meal, he had experienced a severe precordial pain, crushing in character, that radiated down both arms into the fingers and also up into the neck. The pain was attended by dyspnea, cyanosis, cough, and a moderate degree of shock. Large doses of opiates given over a period of 14 hours were necessary to control the pain. He had considered himself in good health prior to the onset and had had no pain or other symptoms referable to the heart. There was no rheumatic history.

When examined there was obvious dyspnea and orthopnea with a moderate degree of cyanosis. The skin, which showed a gray pallor, was moist and cold. The lungs were filled with wet râles. The heart was normal in size. The rhythm was regular and the rate 102 per minute. The heart sounds were distant and of poor quality. A soft, systolic murmur was audible at the apex. The blood pressure was 90 mm. Hg systolic and 62 mm. diastolic. The liver was at the costal margin and there was no evidence of peripheral edema.

He was placed in an oxygen tent and was treated with opiates, aminophyllin, hypertonic glucose and mercurial diuretics. He responded well and was soon quite comfortable and relieved of the dyspnea and cyanosis. A slight elevation in temperature persisted during the first week and the sedimentation rate was increased.

An electrocardiogram taken on May 10, 1939, revealed the following: There was regular sinus rhythm. The rate was 102 per minute. Intervals were normal. $P_1$ was notched and $P_2$ was broadened. QRS was of low voltage in the standard leads. There was left axis deviation. $ST_1$ was isoelectric. $T_1$ was small and inverted. $ST_2$ was slightly elevated. $T_2$ was small but erect. $ST_3$ was isoelectric. $T_3$ was very small and erect. $ST_4$ was displaced upward 0.6 cm. $T_4$ was sharply inverted. $QRS_4$ was monophasic and directed downward. Impression was myocardial infarction, anterior type.

Following the coronary occlusion his recovery was uneventful until August 1939, when he first noted pain of the persistent aching type in the left shoulder and arm. Abduction and external rotation were limited and painful, and there was tenderness in the shoulder joint and in the region of the deltoid insertion. At the time of the shoulder disability he also noted numbness and tingling in the fingers of both hands, associated with stiffness in the phalangeal joints. There was also lividity of the palms of both hands, especially of the palmar surfaces of the fingers. The pain was relatively intractable and persisted in the left shoulder for more than 20 months, disappearing very slowly. Pain appeared in the right shoulder eight months after the onset of the disability in the left shoulder and persisted in that region to a slight degree. The numbness, tingling and stiffness of the hands were of short duration and at no time was redness or swelling noted. However, the discoloration of the palmar surfaces persisted.

In April 1941, palmar changes of the Dupuytren's type were noted for the first time. A small, firm nodule about 1 cm. in diameter had appeared at the base of the ring finger of the right hand. By October 1941 this nodule had increased in size and there was puckering of the overlying skin although no contracture was present. The left palm showed no evidence of changes.

Late in November 1941, for the first time he began to have cramping pains in the calves of both legs. The pains were brought on by walking and were quickly relieved by rest. No changes in the pulsation of the arteries of either leg could be found. The leg pains subsided somewhat but excessive exercise still caused some discomfort.

*Case 3.* T. C., a 46 year old white male, real estate salesman, was seen first on November 27, 1937, when he complained of precordial pain. The pain, which was moderately severe and constricting in character, radiated from the precordium into the right arm and, when especially severe, into both arms. Slight exertion precipitated the pain which had occurred almost daily for the two weeks prior to his first visit. Slight dyspnea on exertion, palpitation, tachycardia and occasional irregularities of cardiac rhythm had been noted. The family history was irrelevant and there was no history of rheumatic fever.

Physical examination at the time of the first visit revealed a blood pressure of 192 mm. Hg systolic and 140 mm. diastolic. There was no evidence of cardiac enlargement. The second aortic sound was accentuated. No murmurs were heard. The cardiac rhythm was interrupted by occasional premature contractions. No evidence of decompensation was found.

An electrocardiogram taken November 27, 1937, revealed the following: There was a normal sinus rhythm. The rate was 92 per minute. Intervals were normal. There was marked left axis deviation. $ST_1$ and $ST_2$ were slightly depressed. $QRS_2$ and $QRS_3$ were slurred. $T_3$ was diphasic. No chest lead was recorded.

While under treatment he remained relatively free from pain until shortly after the death of his wife in November 1938. The pain then recurred with increased frequency and severity and now for the first time awakened him from sleep. Following an especially severe attack of pain of two hours' duration on November 15, 1938, the blood pressure fell from 180 mm. Hg systolic and 115 mm. diastolic to 150 mm. systolic and 100 mm. diastolic, and he was hospitalized. At this time he was very apprehensive, slightly dyspneic, pale and exhausted. Occasional moist râles were heard at the lung bases. The heart was borderline in size. The rate was 93 per minute. The cardiac rhythm was interrupted by frequent premature contractions. The quality of the heart sounds had become poor, and a soft systolic murmur was present at the apex. There was no enlargement of the liver or peripheral edema.

An electrocardiogram taken on November 15, 1938, revealed the following changes: Frequent ventricular premature contractions were present. The T voltage in the standard leads was reduced. $ST_1$ and $ST_2$ were more definitely depressed. $T_1$ was diphasic. $ST_3$was slightly elevated. $T_3$ was diphasic. $ST_4$ was slightly depressed. $T_4$ was inverted. A coronary occlusion with myocardial infarction was suspected.

During the week following there was a slight elevation in temperature and the sedimentation rate was increased. Opiates and intravenous papaverine controlled the severe pain. An electrocardiogram taken at an interval of one week, on November 22, 1938, showed some changes to have occurred during that time. $ST_1$ was slightly depressed and followed by an erect $T_1$ of very low voltage. $ST_2$ was slightly elevated and coved. $T_2$ was inverted and of low voltage. $ST_3$ was elevated to a more marked degree and was definitely coved, followed by a small inverted $T_3$. Lead IV showed no change.

After being without pain for one week, he was discharged to his bed at home on November 25, 1938. He continued quite comfortable and free from pain until the end of December when an attempt was made to get him out of bed by the usual easy stages. At that time the pain recurred with such frequency and severity that it necessitated his return to complete bed rest. Tissue extract was added to the aminophyllin, nitrites and sedatives he had been receiving but without striking response and he was again hospitalized. The findings in the heart remained as on the previous admission. The blood pressure, however, had fallen to 112 mm. Hg systolic and 80 mm. diastolic. There was no elevation of temperature, no leukocytosis, no increase in sedimentation rate at this time. Again an electrocardiogram revealed changes suggesting progressive involvement of the myocardium.

Changes in the palms of the hands were noted for the first time during this admission, although they must have been present for some time prior to this discovery. Attention was drawn to the hands because of pain, swelling and stiffness of the finger joints. In the left palm, at the base of the ring and little fingers, definite thickening and puckering of the skin was found but without evidence of contracture. On the right, again at the base of the ring and little fingers, thickening and puckering of the skin of more marked degree was noted and a beginning contracture was present. Motion of the fingers, although painful, was complete except for the ring and little fingers of the right hand which could not be extended completely. Some bluish mottling of the palms and palmar surfaces of the fingers was noted. At no time were the shoulders the site of the aching constant type of pain. However, during the attacks of precordial pain, the pain in the hands was usually aggravated. On several occasions the pain originated in the hands and radiated to the precordium.

In spite of all therapy the attacks of pain continued to occur from eight to 12 times daily and he finally sought relief elsewhere on March 8, 1939. He received some temporary relief there while being given "Cortiode" but on April 23, 1939, during a severe attack of pain, he died.

Pertinent necropsy findings were as follows: The heart weighed 430 grams. The coronary arteries were thickened with numerous calcified areas throughout, especially in the anterior descending branch of the left coronary artery. This vessel was completely occluded 2 cm. from its orifice by a fresh thrombus. The right coronary artery showed considerable thickening and calcification but was patent throughout. An old organized thrombus was found at the tip of the left ventricle and the cut surface showed much scarring in that area. The valves of the heart were not remarkable.

At practically every orifice of the smaller arteries coming off of the aorta, there was marked nodular thickening with considerable plaque formation and longitudinal streaking.

The microscopic examination showed marked arteriosclerotic changes in practically all tissues examined.

*Case 4.* N. J., a 60 year old, white male, a retired executive, had suffered from substernal pain for five months when seen for the first time on July 9, 1937. The pain, severe and constricting in character, radiated from the upper sternum into both arms. The episodes of pain, varying in duration from 15 minutes to one hour and occurring from one to three times daily, were precipitated by exertion. Especially severe attacks were accompanied by mild nausea and moderate dyspnea.

At the age of 46 years the patient was said to have had "inflammatory rheumatism" and had been told that the heart had become involved. He had retired at 50 years of age and had done no work since.

Examination at the time of the first visit revealed a moderately obese male, quite well preserved. There was no evidence of exceptional arteriosclerosis. The heart was enlarged to the left and downward. The rhythm was regular with a rate of 92 per minute. The heart sounds were distant and a soft systolic murmur was heard at the apex. The blood pressure was 190 mm. Hg systolic and 90 mm. diastolic. There were no signs of congestive failure.

An electrocardiogram taken July 10, 1937, showed regular sinus rhythm with a rate of 90. The PR interval was prolonged to 0.24 second. $P_2$ was notched. The QRS was slurred in the standard leads with marked splintering in Lead III. $T_1$ was inverted. There was no significant displacement of ST in any lead. $T_2$ and $T_3$ were erect. The fourth lead was not recorded. The electrocardiographic findings were considered to be due to coronary sclerosis and the resultant myocardial ischemia. There was little to substantiate a diagnosis of rheumatic heart disease.

Under treatment he remained fairly comfortable except for occasional attacks of pain until early in 1941. In July 1941, after not having been seen for some time, he complained of extreme dyspnea, repeated severe attacks of precordial pain, disagreeable palpitation, cough, orthopnea, swelling of the ankles and excessive fatigue, all of which had been present for several months. His condition had become so desperate that he hesitated to seek aid because of his fear of what the prognosis might be.

At this time physical examination revealed auricular fibrillation and advanced cardiac decompensation.

An electrocardiogram recorded August 1, 1941, revealed the following: Auricular fibrillation was present. QRS was slurred in all leads. $QRS_3$ and $QRS_4$ showed notching. $ST_1$ was slightly depressed. $T_1$ was inverted and of very low voltage. $ST_2$ was depressed. $T_2$ was inverted. $ST_3$ and $T_3$ were isoelectric. $QRS_4$ was monophasic with no Q or S element. $ST_4$ was elevated very slightly. $T_4$ was

erect but of low voltage. It was thought that myocardial infarction probably had occurred some time during the previous three months.

Although he was unaware that changes had taken place in his hands, small, firm nodules were present at the bases of both ring fingers. The nodules were about 0.8 cm. in diameter and were not adherent to the deeper structures. There was no contracture and he had not noted pain, swelling or circulatory changes in the hands. Careful questioning failed to disclose a history of shoulder pain other than that referred to the shoulder from the precordium during attacks of angina pectoris.

Subsequently during the course of digitalization he developed a hemiplegia, probably due to cerebral embolism, and died.

*Case 5.* F. J., a 59 year old, white male, a mechanic, was seen for the first time in June 1941, when he complained of precordial aching, dizziness and shortness of breath on exertion. During the previous winter he had noted dyspnea, substernal oppression and non-productive cough, brought on by exertion during cold weather. In May 1941, while at work, he suddenly became dyspneic and lost consciousness for an unknown period. In spite of the weakness and excessive fatigue that persisted after this experience he returned to his work. About four weeks later he experienced a similar episode on the way home from work, becoming dyspneic and cyanotic and losing consciousness for about 20 minutes. Oxygen was administered by a "rescue squad" and he was removed to his home. Dyspnea when at rest and some substernal aching persisted but he again returned to work until the severity of his symptoms made it impossible for him to continue. He was seen for the first time 10 days after the last episode.

Physical examination revealed a well developed and slightly obese white male who was dyspneic on slight exertion. The mucous membranes were slightly cyanotic. The neck veins were distended moderately. Moist râles were heard at both lung bases. The heart was enlarged to the left and downward. The rhythm was regular with a rate of 108 per minute. The heart sounds were of only fair quality with a rough, high-pitched systolic murmur at the aortic area, transmitted to the apex. The blood pressure was 146 mm. Hg systolic and 82 mm. diastolic. The liver edge was at the right costal margin and minimal pretibial edema was noted.

An electrocardiogram taken on June 20, 1941, revealed regular sinus rhythm and normal intervals. There was marked left axis deviation. The QRS was slurred slightly in all leads. $ST_1$ was depressed with an inverted and coved $T_1$. $ST_2$ was depressed with a diphasic $T_2$. $ST_3$ was elevated with an erect and coved $T_3$. $ST_4$ was depressed with a diphasic $T_4$. It was the impression that infarction of the myocardium had occurred recently.

The past medical history was irrelevant with the exception of painful swelling of the ankles at 28 years of age, which had necessitated two weeks of bed rest. The details of this illness were obscure.

Under treatment his condition improved and he remained quite comfortable until early in August when he noted pain and stiffness in the shoulders and pain over the lateral aspect of the upper arm. The shoulder disability was soon followed by stiffness, swelling and numbness in both hands. Redness and lividity were not noted. In October thickening of the skin of the palms was observed. The right palm was involved at the base of the index and of the little fingers where the depth of the normal palmar folds was increased and the skin had become puckered. The left palm showed similar changes at the base of the ring finger. The condition has been slowly progressive since that time.

*Case 6.* R. S., a 70 year old, white housewife, was seen for the first time on May 25, 1941, complaining of pain in the left upper abdomen, nausea, vomiting and prostration. The temperature was elevated to 100.6° F., and there was a leukocytosis. The cardiac findings were essentially negative. The heart was regular with a rate

of 70 per minute. The blood pressure was 100 mm. Hg systolic and 72 mm. diastolic.

On the following day the pulse rate had increased to 110 per minute, and there were occasional premature contractions. At this time a systolic murmur was heard over the apex and there was also a pericardial friction rub in this area.

An electrocardiogram taken on May 26, 1941, showed the following: Regular sinus rhythm was present with the rate of 100 per minute. QRS was slurred in the standard and chest leads. $ST_1$ was slightly elevated. $T_1$ was inverted and of low voltage. $ST_2$ was isoelectric. $T_2$ was erect. $ST_3$ was isoelectric. $T_3$ was erect. $QRS_4$ was monophasic and inverted. $ST_4$ was elevated with inverted $T_4$. The interpretation was myocardial infarction.

After two weeks of satisfactory progress the patient became desperately ill. There were now frequent episodes of auricular fibrillation which were imperfectly controlled by quinidine sulphate. Oxygen was administered continuously by nasal catheter. This situation persisted for several weeks.

In the intervals between the episodes of auricular fibrillation the patient's pulse was rapid, thready, and showed many runs of premature contractions. The blood pressure remained at 90 mm. Hg systolic and 50 mm. diastolic except for several occasions when the systolic level fell below 80 mm. About 10 weeks after the onset a gradual improvement was noted. The episodes of auricular fibrillation became shorter in duration and occurred less frequently. The systolic blood pressure approached a level of 100 mm. Hg and, with the attending gain in strength, the oxygen was no longer necessary. The pulse, between the episodes of fibrillation, became slower, more regular and more forceful.

At this time the patient began to complain of pain in both shoulders, both hands and both knees. Some stiffness of the fingers and hands was also noted. During the next six weeks thickening of the palmar surfaces of both hands developed. The pain diminished but the stiffness persisted. The changes in the palmar fasciae progressed slowly during the next four or five months until definite contractures were present. The pain in the shoulders was not constant but recurred several times. At no time was swelling, redness or lividity of the hands noted. A visible and palpable ridge, extending from the thumb into the palm formed in both hands, being more marked in the left palm. The skin of the entire palm became thickened and hardened bilaterally. The condition has been stationary during the past two or three months. Pain and stiffness in the knees recurred at times but diminished in severity. No plantar changes were observed.

The patient subsequently improved clinically. The blood pressure rose to 120 mm. Hg systolic and 70 mm. diastolic and fibrillation had not occurred, although occasional premature contractions were noted. When last seen, seven months after the onset, she was able to be up and about for short intervals. She was asymptomatic except for some stiffness in fingers and hands.

An electrocardiogram of December 14, 1941, showed regular sinus rhythm with a rate of 76 per minute. QRS voltage had increased in Leads I and II. $ST_1$ and $T_1$ were isoelectric. $ST_2$ was slightly depressed with $T_2$ erect. $ST_3$ was slightly depressed with $T_3$ erect. $ST_4$ was isoelectric. $T_4$ was inverted and of low voltage. $QRS_4$ was monophasic and erect.

## Discussion

The changes in the palmar fasciae, closely resembling Dupuytren's contractures, and the coronary vascular accident bear a definite relation to each other. Changes in the palms had not been noted in any instance before the onset of the cardiac difficulty. The coronary occlusion, therefore, ap-

parently acts in some obscure manner as the precipitating factor. In the cases presented Dupuytren's contracture appears to be a complication of or a sequel to coronary occlusion, as well as the shoulder disability described by several authors,[2, 3, 4] and the hand syndrome as noted by Askey.[1]

The palmar changes, as noted in the cases here presented, appear typical of Dupuytren's contracture. The first finding is ordinarily a firm nodule in the palmar aponeurosis, most often in the ulnar area near the metacarpophalangeal joint. The process is slowly progressive, gradually extending to involve the entire palmar fascia but allowing the tendons to escape. Due to the fibrosis and contracture of the underlying fascia and to the loss of subcutaneous fat the skin appears thickened, folded, hard and closely adherent. Although the contracture does not appear in both hands simultaneously, it frequently becomes bilateral. The typical course is slow but

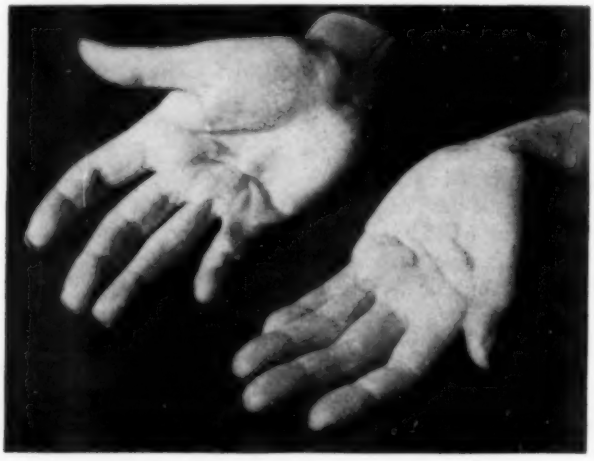

FIG. 1.

continuous and in the advanced stage results in permanent flexion of one or more fingers to a variable degree. Although there is an early limitation of extension further voluntary flexion is not limited or painful (figure 1).

Of the 21 cases showing the painful hand syndrome described by Askey,[1] seven showed changes in the palmar fasciae which resembled the early stage of Dupuytren's contracture. In these cases, however, the process failed to progress to the stage of contracture and a regression was noted in two cases. In none of the six additional cases here reported has there been any evidence of regression of the palmar changes. Moreover, in three cases (cases 1, 3, and 6) definite contractures have developed, and in each case the contractures appeared bilaterally. Although death limited the period of observation in two of the cases, the lesions have been slowly progressive with only one exception. In case 6, after going on to ridge formation and early contracture, the process has become stationary.

In five instances other symptoms and objective findings referable to the hands were noted (table 1). Pain, stiffness, swelling, livid discoloration, numbness, tingling, and coldness were observed. Stiffness, which was the most common finding, was complained of in four instances. Pain occurred in three cases and was associated with stiffness whenever found. Bluish discoloration, numbness and tingling were each found in three cases. Swelling was noted in two cases but no history of redness could be obtained nor was redness observed. Coldness of the hands was found only once. The color changes and associated paresthesias bear out Askey's statement

TABLE I

| Case | Occupation | Shoulder Disability | Time of Onset | Objective and Subjective Changes in Hands | Rheumatic History | Arteriosclerosis | Course |
|---|---|---|---|---|---|---|---|
| P. H. 48 yrs. | laborer | severe bilateral | 3 mos. after occlusion | marked bilateral contractures; pain, stiffness, numbness, tingling, discoloration, and coldness | migratory joint pains 18 yrs. | marked as shown in physical examination | progressive to advanced stage |
| T. B. 40 yrs. | advertising executive | severe bilateral | 11 mos. after occlusion | small nodule, right hand only, discoloration, numbness, and tingling | none | none | slowly progressive |
| T. C. 46 yrs. | real estate salesman | none | uncertain | bilateral contractures; pain, swelling, stiffness, and discoloration | none | marked generalized as shown in autopsy | progressive until time of death |
| N. J. 60 yrs. | retired executive | none | uncertain | bilateral nodules, no contractures | inflammatory rheumatism 46 yrs. | commensurate with age | short period of observation |
| F. J. 59 yrs. | mechanic | bilateral | 5 mos. after occlusion | bilateral nodules, no contractures; stiffness, numbness, and swelling | painful swollen ankles at 28 yrs. | commensurate with age | slowly progressive |
| R. S. 70 yrs. | housewife | bilateral recurrent | 4 mos. after occlusion | bilateral contractures; pain, stiffness, and thickening over entire palm | none | none | stationary, no regression |

that the sympathetic nerves may well play a predominant rôle in this condition.

The relation of the time of the coronary incident to the onset of the palmar changes was variable. In two cases it could not be determined accurately, but in the remaining cases it varied from three to 11 months, being three, four, five, and 11 months in the known instances.

Although all of Askey's cases with palmar changes demonstrated the painful shoulder and hand syndrome, two of the cases here presented gave no history of shoulder disability and no objective or subjective hand findings were noted in one. However, one case which gave no history of shoulder complaints did suffer from pain, swelling and stiffness of the fingers. No cases of unilateral shoulder pain were observed. In addition to the pain and stiffness in the shoulders and hands, one patient complained of pain in the knees. There has been no evidence of plantar changes in this case to date.

Although the onset of the Dupuytren's contracture did not occur at the same time in both hands, the lesion became bilateral during the period of observation in five instances. One patient who experienced a long disability in both shoulders developed palmar changes in the left hand only.

In this small series there appears to be little to support the etiological relationship of Dupuytren's contracture to either acute or chronic trauma of the palmar aponeurosis as suggested by some.[5] No history was obtained in any case to support the theory of an hereditary factor.[6] In three instances the occupation was such as to eliminate the consideration of trauma as an etiological factor. In the remaining three cases, those of the laborer, the mechanic, and the housewife, in spite of any possible exposure to trauma, the palmar aponeurosis showed no evidence of thickening until after the coronary thrombosis.

Whether the extensive generalized arteriosclerosis found in one case at necropsy and in another case at physical examination is of significance is impossible to determine in the light of the present incomplete knowledge. It is also to be noted that three patients gave histories of joint pains at an earlier age. The details of these rheumatic episodes are not as complete as could be desired but in two instances acute rheumatic fever is suggested. Whether this is significant is problematical and can be determined only by further observation.

In 1929 Nippert[7] advanced the theory that Dupuytren's contracture developed on the basis of an increase in sympathetic tone. More recently Hale Powers[8] has explained the palmar phenomenon on the basis of irritation and hyperexcitability of the sympathetics due to visceral disease which he indicates is frequently intrathoracic. He placed Dupuytren's contracture in the same category as pulmonary hypertrophic osteoarthropathy, scleroderma and other trophic disturbances. The mechanism by which visceral disease precipitates dystrophies at the periphery is thought to be through irritation of the sympathetic ganglia. Powers also called attention to the association of Raynaud's disease and Dupuytren's contracture. As an explanation of the usual localization of the palmar changes in the ulnar area, he points out that the ulnar nerve bears a more intimate relation to the intrathoracic sympathetic ganglia than the other nerves of the brachial plexus.

Although the mechanism cannot be explained with certainty, the sympathetic nervous system appears to play a part as evidenced by the associated paresthesias and color changes.

## Summary

1. Six cases of Dupuytren's contracture as a sequel of coronary occlusion are presented.

2. Dupuytren's contracture may be associated with the syndrome of shoulder disability and painful hands following myocardial infarction.

3. The palmar changes in the cases presented appear to be typical of Dupuytren's contracture in its various stages.

4. Three cases progressed to the stage of contracture and in no case was regression noted.

5. Pain, stiffness, swelling, livid discoloration, numbness, tingling, and abnormal skin temperature of the hands may be associated with the palmar changes.

6. The etiology and pathogenesis are not understood, but irritation of the sympathetic ganglia may play an important etiological rôle.

I wish to thank Dr. G. C. Owen, Oshkosh, Wisconsin, for the privilege of including case 6, in this series.

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# CARDIOVASCULAR SYPHILIS: AN APPROACH TO EARLY CLINICAL RECOGNITION AND EARLY TREATMENT *

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The aim of the syphilologist and the clinician is to prevent cardiovascular syphilis by early and adequate treatment of the primary infection; the aim of the syphilologist, the cardiologist, and the clinician is to recognize and treat cardiovascular syphilis in its earliest form and as early as possible, in order to prevent the complications that may arise therefrom. Although the former depends primarily on the education of the patient who must seek early treatment and avoid delinquency of treatment, the latter depends primarily on the education of the physician who must be alert to the recognition of this condition.

Syphilis ranks fourth as the cause of cardiovascular disease, following arteriosclerosis, hypertension, and rheumatic fever. Heart disease due to syphilis is the only one whose etiologic agent is definitely known and for which preventive measures are not only known but are available. According to Blumgart,[1] cardiovascular syphilis is responsible for more adult deaths than is neurosyphilis, and constitutes 10 to 15 per cent of all cardiovascular disease. Approximately 5 per cent of all patients who come to autopsy in general hospitals show evidence of cardiovascular syphilis,[2] and of all patients with syphilis, 55 to 86 per cent show syphilitic involvement of the cardiovascular apparatus as revealed at autopsy.[3] One third of the sudden deaths due to heart disease are the result of cardiovascular syphilis.

Leiby, Callaway, and Fleming [4] state that it has been estimated that between 30,000 and 40,000 deaths occur annually from cardiovascular syphilis. According to them, the life expectancy of patients with cardiovascular syphilis ranges from one to 10 years among patients with extensive involvement of the aorta to that of a normal lifetime for those with uncomplicated syphilitic aortitis who receive adequate treatment.

Of all the diseases of the cardiovascular system, uncomplicated syphilitic aortitis is the most frequently overlooked, and yet it is the most common form of visceral syphilis (70 per cent).[5] This may be due to a silent phase of the disease which no doubt depends upon the extent and distribution of the pathologic process, and a clinical diagnosis is, therefore, impossible. However, a more important reason for this oversight is probably the inability of the physician to evaluate the early clinical signs, and to bear in mind the possibility of this condition.

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## Purpose

This study was undertaken for two reasons: (1) because of the confusion existing in the current literature concerning the difficulty or impossibility of making a clinical diagnosis of uncomplicated syphilitic aortitis, and (2) to evolve a method of early clinical recognition if possible.

According to White and Wise,[6] a clinical diagnosis of aortic syphilis can rarely be made within 10 years after infection, and therefore the early diagnosis of cardiovascular syphilis is impossible. Cabot and Adams [7] claim that syphilis of the aorta cannot be recognized clinically unless there is an appreciable degree of aortic valve involvement or considerable dilatation of the aorta with or without actual aneurysm. Garvin [8] believes that uncomplicated syphilitic aortitis is a disease virtually without symptoms or signs. According to the criteria of the New York Heart Association,[9] uncomplicated syphilitic aortitis frequently escapes clinical recognition since it seldom produces symptoms, but evidences of its presence may be found within three to 10 years after the chancre.

The prerequisites for this study are (1) to examine patients with proved syphilis, (2) to examine a large series of patients, (3) to have a single examiner see these patients, and (4) to corroborate the clinical diagnosis by instrumental methods, by follow-up study to discover complications, and by postmortem examination. All these prerequisites were fulfilled in this study with the exception of postmortem examinations, because these cases were followed in a large social hygiene clinic of the New York City Health Department where there are no hospital facilities.

## Material and Method of Study

This paper is a preliminary report of the study of 1270 cases of proved syphilis over a period of two years. In a subsequent paper we will be able to give more detailed data on the follow-up study to discover complications, and add more cases to our series.

All patients were examined by one of us (M.D.). No attempt was made to select the cases. They were referred for cardiovascular check up for the following reasons: (1) prior to starting arsenic therapy in latent asymptomatic cases, (2) because of the advanced age of the patient, (3) as a newly admitted case, (4) because of complaints referable to the cardiovascular system (very few), and (5) as a case of congenital syphilis.

The routine history consisted of the following questions: (1) dyspnea on exertion (great emphasis was placed on evaluating this symptom correctly); (2) paroxysmal nocturnal dyspnea; (3) precordial or substernal pain (pain in other areas (as the spine) was investigated); (4) ankle or leg edema (peripheral vascular and orthopedic conditions were ruled out); (5) cough or hemoptysis; (6) dysphagia; (7) dysphonia; (8) other etiologic factors were sought for (rheumatic fever, hypertension, etc.).

The routine physical examination consisted of the study of (1) the pulse and blood pressure in both upper extremities; (2) the peripheral and neck vessels, including the suprasternal (episternal) notch; (3) the chest wall for pulsations, thrills, or deformities; (4) the size of the heart and aorta by percussion; (5) the auscultatory signs of the anterior and posterior chest (heart and lungs), including the mitral, pulmonic, and aortic areas, with emphasis on the character of the sounds, the intensity of the sounds, and the presence or absence of murmurs. When the base of the heart was examined, the patient was placed in the erect sitting position (bending slightly forward) and auscultation was performed in forced expiration.

Fluoroscopy and roentgenography were used only under the following conditions, and not as a routine in all the cases of syphilis examined: (1) a definite clinical diagnosis of uncomplicated aortitis; (2) the presence of the complications of cardiovascular syphilis; (3) the suspicion of the presence of cardiovascular syphilis; (4) if hypertension or other diseases of the heart were present.

In a preliminary examination of a certain number of cases of proved uncomplicated aortitis and aortic insufficiency, it was noted that the aortic second sound was heard best in many instances over the third right intercostal space near the sternum and in some cases over the fourth right intercostal space, and not as anticipated over the conventional second right intercostal space. Furthermore, it was also noted that in some cases a systolic murmur (as well as a diastolic murmur) was heard best over the third left intercostal space near the sternum, and at times was only heard over this area. In most cases the systolic murmur was heard over the second, third, or fourth right sternal space or in more than one of these areas. This proved that in many instances the change in the character of the aortic second sound, as well as murmurs, may be overlooked if examination of these areas is omitted, thereby missing the clinical diagnosis of uncomplicated aortitis. Another point of interest in physical diagnosis was the importance of comparing the character of the aortic second sound with that of the pulmonic second sound as well as the intensity of these sounds.

According to the criteria of the New York Heart Association,[9] hypertension is present when the systolic blood pressure is persistently above 140 mm. Hg or the diastolic above 90 mm. Hg. In order to avoid any question of borderline cases, hypertension was considered present in this study with a systolic pressure above 150 mm. Hg or a diastolic above 100 mm. Hg.

The cases found to show evidence of uncomplicated aortitis were divided into two groups: those 40 years of age or younger, and those over 40 years, because in the latter group arteriosclerosis cannot be excluded, and one cannot be certain whether dilatation of the aorta is due to aortitis, arteriosclerosis or a combination of both. Aortic sclerosis may also give rise to the characteristic aortic second sound which cannot be differentiated from that of aortitis.

## Results

Of the 1270 cases of syphilis examined, 304 (24 per cent) were diagnosed clinically as uncomplicated syphilitic aortitis, and 390 (30.7 per cent) constituted the entire group of cardiovascular syphilis. Among the 390 cases, there were 304 (78 per cent) cases of uncomplicated aortitis, 37 (9 per cent) cases of aortic insufficiency, 19 (5 per cent) cases of aortic insufficiency plus aneurysm, and 4 (1 per cent) cases of coronary ostial stenosis. There were 245 (63 per cent) male patients, 145 (37 per cent) female patients, 255 (65 per cent) white patients, and 135 (35 per cent) negro patients. In other words the proportion of males to females was approximately 2:1, and that of the white to the negro race approximately the same.

Table 1 shows the admission diagnosis of the 390 cases of cardiovascular syphilis. It will be noted that only 72 cases exhibited evidence of cardiovascular syphilis on admission. The other 318 cases developed their cardiac lesions while under observation.

TABLE I

Analysis of Admission Diagnosis of 390 Cases of Cardiovascular Syphilis

| Admission Diagnosis | Number of Cases | % |
|---|---|---|
| Primary | 3 | 0.7 |
| Secondary | 9 | 2.4 |
| Early Latent (asymptomatic) | 21 | 5.5 |
| Late Latent (asymptomatic) | 240 | 61.5 |
| Central Nervous System | 32 | 8.2 |
| Cardiovascular | 72 | 18.5 |
| Congenital | 8 | 2.0 |
| Gumma of Bone | 3 | 0.7 |
| Tertiary Skin | 2 | 0.5 |
| Total | 390 | 100.0 |

In analyzing the 304 cases of uncomplicated aortitis by decades, 275 (90.4 per cent) occurred between the ages of 21 and 60, and the cases were just as frequent in the third decade as in the fifth. In the age group 40 years or younger, there were 148 (48.7 per cent) cases, and in the group over 40 years, there were 156 (51.3 per cent) cases (table 2). Levitt and Levy [10] in their study of 508 cases of syphilitic aortic disease found that 78.8 per cent of the total number occurred between 31 and 60 years of age.

In further analyzing this group of 304 cases, the proportion of males to females is approximately 2:1. The Coöperative Clinic reports syphilitic aortic disease three times more common in the male than in the female. Other clinics report as high as 5:1. Uncomplicated aortitis is proportionately twice as common in the negro race as in the white in the group 40 years of age or younger, and more common in the negress than in the others (male negro, male and female white). In the older group the white male predominates followed in order by the white female, negro male and negress

TABLE II

Analysis of 304 Cases of Uncomplicated Syphilitic Aortitis by Decades

| Age | Number of Cases | % |
|---|---|---|
| 1–10 | 0 | 0.0 |
| 11–20 | 6 | 2.0 |
| 21–30 | 73 | 24.0 |
| 31–40 | 69 | 22.7 |
| 41–50 | 73 | 24.0 |
| 51–60 | 60 | 19.7 |
| 61–70 | 21 | 7.0 |
| 71–80 | 2 | 0.6 |
| Total | 304 | 100.0 |

(table 3). Musser[11] observes that central nervous system manifestations are less likely to occur among the negro race than are the cardiovascular, and that, therefore, the vasotropic strain of spirochete would be more prevalent among this race than the neurotropic. According to Turnville[2] cardiovascular syphilis is two to three times more prevalent among negroes than among whites, and he explains this by the prevalence of syphilis among negroes, lack of adequate treatment and the fact that they are more apt to do heavy manual labor. We believe that the negro acquires his syphilis earlier in life than the white and that this accounts for the prevalence of cardiovascular syphilis, especially in the younger age group.

TABLE III

Uncomplicated Aortitis in Relation to Age Group, Sex, and Race

| Age Group | Total No. Cases—304 | | | | White—182 (59.8%) | | | | Negro—122 (40.2%) | | | | Total | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | | Female | | Male | | Female | | Male | | Female | | | |
| | Cases | % | Cases | % | Cases | % | Cases | % | Cases | % | Cases | % | | |
| 40 yrs. or Younger | 82 | 27.0 | 66 | 21.7 | 42 | 23.1 | 24 | 13.2 | 40 | 32.7 | 42 | 34.5 | 148 | 48.7 |
| Over 40 | 108 | 35.5 | 48 | 15.8 | 86 | 47.3 | 30 | 16.4 | 22 | 18.1 | 18 | 14.7 | 156 | 51.3 |
| Total | 190 | 62.5 | 114 | 37.5 | 128 | 70.4 | 54 | 29.6 | 62 | 50.8 | 60 | 49.2 | 304 | 100.0 |

Neurosyphilis was present in 104 (26.6 per cent) of the 390 cases of cardiovascular syphilis with males predominating over females two to one, and whites over negroes five to one. The frequency of central nervous system syphilis in cardiovascular syphilis is given as 10 per cent by Riven and Feigenbaum[12] and as 16–20 per cent by White.[13]

Relative to the history of the primary infection, 128 (32.8 per cent) of the 390 cases of cardiovascular syphilis remembered the chancre, whereas 262 (67.2 per cent) gave a negative history. Of those who remembered the chancre, uncomplicated aortitis was diagnosed within 10 years after the primary infection in 38 cases, of which 24 were negroes and 14 were white

patients. They were classified as follows in the order of years after the chancre: first year—one case; second year—three cases; third year—three cases; fourth year—three cases; fifth year—five cases; sixth year—three cases; seventh year—six cases; eighth year—five cases; ninth year—four cases; tenth year—five cases.

A study of the relationship between hypertension and cardiovascular syphilis showed that 185 (47.4 per cent) of the 390 cases of cardiovascular syphilis had hypertension. Among the 304 cases of uncomplicated aortitis there were 134 cases (44 per cent) of hypertension (table 4). In order to determine whether these figures were coincidental, the balance of the 1270 syphilitics or 880 cases was used as a control group. Among this group there were cases without cardiac disease, with arteriosclerotic heart disease,

TABLE IV

Analysis of Number of Cases of Hypertension Among 390 Cases of Cardiovascular Syphilis

| Race | Sex | Uncompl. Aortitis | Aortic Insuff. | Aortic Insuff. plus Aneurysm | Aneurysm | Cor. Ost. Stenosis | Total |
|---|---|---|---|---|---|---|---|
| White | M | 59 | 12 | 0 | 10 | 2 | 83 |
| | F | 27 | 9 | 1 | 2 | 1 | 40 |
| Negro | M | 19 | 2 | 2 | 1 | 0 | 24 |
| | F | 29 | 5 | 0 | 4 | 0 | 38 |
| Total | | 134 | 28 | 3 | 17 | 3 | 185 |

hypertensive heart disease, rheumatic heart disease, and congenital heart disease. Hypertension was present in 100 cases (11.3 per cent). In other words, in this large series of syphilitics, hypertension was four times as common among those with cardiovascular syphilis as among the cases without cardiovascular syphilis. To determine further whether this was a coincidental finding and depended entirely upon the presence of hypertension in the older age group, it was found that 50 cases (27 per cent) occurred in the group 40 years or younger. Of this number, 18 (29.1 per cent) were negresses, 12 (19.3 per cent) were male negroes, 11 (8.9 per cent) were white males, and nine (7.4 per cent) were white females. Although hypertension is quite a common finding among negroes, in the older age group the whites overshadowed the negroes by 103 cases (76.3 per cent) to 32 cases (23.7 per cent), a proportion of over three to one, even though the proportion of whites to negroes in the entire group of cardiovascular syphilis was less than two to one (table 5). This proved that the large percentage of hypertension did not depend solely upon the negroes.

There were 50 cases of congenital syphilis among the 1270 cases of syphilis examined. Of these, eight cases (16 per cent) showed definite clinical evidence of uncomplicated aortitis. The ages of the positive cases varied between 13 and 40 years with an average of 20 years. All but one showed evidence of varying degrees of dilatation of the ascending aorta by

fluoroscopy and roentgenography. Coincidently there were four cases of congenital heart disease among the 50 congenital syphilitics. Among the eight cases of congenital cardiovascular syphilis, there were two cases (25 per cent) of neurosyphilis.

Of the 304 cases of uncomplicated aortitis, five (1.6 per cent) showed no evidence of a dilated aorta by fluoroscopy and roentgenography, and one of these had congenital syphilis. The clinical diagnosis of aortitis was unmistakable in this group.

There were 12 cases (with ages ranging between 48 and 55 years) that showed clinical evidence of hypertensive-arteriosclerotic heart disease. When examined by fluoroscopy and roentgenography, each showed the presence of an aneurysm. These cases were not included in our series but are mentioned

TABLE V

Hypertension in Relation to Age Group, Race, and Sex

| Age Group | White—123 (66.5%) | | | | Negro—62 (33.5%) | | | | Total | % |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | | Female | | Male | | Female | | | |
| | Cases | % | Cases | % | Cases | % | Cases | % | | |
| 40 yrs. or Younger | 11 | 8.9 | 9 | 7.4 | 12 | 19.3 | 18 | 29.1 | 50 | 27 |
| Over 40 | 72 | 58.5 | 31 | 25.2 | 12 | 19.3 | 20 | 32.3 | 135 | 73 |
| Total | 83 | 67.4 | 40 | 32.6 | 24 | 38.6 | 38 | 61.4 | 185 | 100 |

to demonstrate the value of instrumental means in making a diagnosis of cardiovascular syphilis.

There were nine cases of rheumatic heart disease and one case of congenital heart disease associated with cardiovascular syphilis in this series. The congenital case was most interesting and unique in that it was one of dextrocardia with complete situs inversus in a woman 43 years of age. The diagnosis of uncomplicated aortitis and congenital heart disease was made clinically and verified by instrumental means.

All cases of complicated cardiovascular syphilis presented one or more symptoms with the exception that most of the early and moderately advanced aneurysms were symptomless. None of the cases of uncomplicated aortitis presented any symptoms unless they were associated with other types of heart disease (hypertensive, functional heart disease, etc.).

Of the 390 cases of cardiovascular syphilis, 12 (3 per cent) received early adequate treatment, 20 (5 per cent) received late adequate treatment, and 90 (23 per cent) were delinquent in treatment at one time or another.

## DISCUSSION

Moore and Metildi [14] define uncomplicated syphilitic aortitis as a diffuse supravalvular involvement of the aortic wall, with or without dilatation, but

without valvular incompetency or saccular aneurysm. It is obvious from this definition that uncomplicated syphilitic aortitis may be present without a dilated aorta. According to White and Wise,[6] the first few centimeters of the aorta are commonly first affected by syphilis, and dilatation of this portion, unless extreme, cannot be made out, even by roentgenographic examination, because it is located in the midst of the base of the heart. Maynard [15] reports that of 20 autopsied cases of syphilis, two of three who were thought to have normal aortas showed no disease whereas the third showed syphilitic aortitis, and he comments that to make the diagnosis of uncomplicated aortitis, dilatation of the aorta must be established beyond reasonable doubt. It appears, therefore, from this report that aortitis may be present in a normal sized aorta but to make a diagnosis (by fluoroscopy or roentgenography) the aorta must be dilated.

Is a clinical diagnosis of uncomplicated aortitis impossible in the presence of a normal sized aorta? From our observations we believe that such a diagnosis is possible, and have, therefore, established the following criteria for clinical diagnosis in patients 40 years of age or younger:

(1) The presence of a characteristic aortic second sound. This sound may be described as tambour, drum-like, tympanitic, or hollow, and is usually heard over the second or third right sternal space, and sometimes over the fourth space.

(2) The presence of a systolic murmur over the aortic area (second, third, or fourth right sternal space, over the sternum, the third left sternal space, or in more than one of these areas). A systolic murmur has been heard in many instances over the mitral area.

(3) The presence of suprasternal (episternal) pulsations. This sign indicates elongation and dilatation of the aortic arch.

(4) The presence of increased retromanubrial dullness in the second intercostal space. This sign is of value only when the aortitis is far advanced, and there is moderate or marked widening of the aorta.

(5) The presence of hypertension as a diagnostic aid. Both systolic and diastolic pressures are elevated.

(6) Corroboration of the clinical findings by the use of fluoroscopy and roentgenography to demonstrate the presence or absence of a widened aorta.

According to Carter and Baker,[16] the presence of the characteristic aortic second sound at the aortic area means definite structural change at the aortic ring or at the very origin of the ascending arch or both. This change in tone does not depend upon blood pressure increase. Parsonnet and Bernstein [17] claim that the presence of a bell-like or tambour quality second aortic sound in an individual of 30 or thereabouts may be regarded as almost pathognomonic of uncomplicated syphilitic aortitis. Musser [11] believes that the most valuable physical finding, in fact any finding objective in nature, is the characteristic second aortic sound in the diagnosis of syphilitic aortitis.

The fact that the characteristic aortic second sound is often heard at the

third right sternal space and sometimes at the fourth right sternal space indicates a change in the normal topography of the aorta and heart. According to Dressler,[18] changes in one section of the heart exert an effect on the shape and topography of adjacent portions, displacing them from their normal position and distorting their contours. It is our opinion, therefore, that as the aorta dilates and elongates, the anatomic position of the aortic valve is altered, thereby causing the transmission of sound to areas other than the conventional aortic area.

It is admitted that recognition of the characteristic second aortic sound requires an experienced ear just as Dressler and Moskowitz[19] have demonstrated that in obstetrics auscultation requires acuity of hearing at low frequencies, since in certain cases the ear is incapable of detecting fetal heart sounds. Nevertheless, if one is alert to this condition, experience will come with the recognition of individual cases.

The presence of hyperthyroidism or any condition that can cause a tachycardia may produce the characteristic aortic second sound as well as a systolic murmur. This is due to the increased stroke volume which will increase the velocity of the blood at the semilunar valve orifices, thereby producing alteration in the acoustic qualities. Under such conditions both the aortic and pulmonic second sounds have the same quality, and by comparing these sounds aortitis will be ruled out.

The systolic murmur which occurs with any degree of dilatation (slight, moderate, or marked) at the aortic area is due to the fact that the blood leaving the left ventricle in systole enters a wider chamber and sets up abnormal vibrations. In other words there is an ejection of the blood column during systole through the normally constricted aortic ring into an abnormally dilated aorta. Leiby, Callaway, and Fleming[4] believe that the systolic murmur of an early aortitis may be due to a roughened intima, a dilated aorta with changes in the sounding structure, or a combination of these.

In the beginning the systolic murmur is soft and is usually not transmitted. Later in the disease the murmur becomes rough and harsh and is transmitted into the vessels of the neck, and down along the left sternal border. Occasionally the murmur may be heard at the apex, and we believe that it is transmitted from the aortic area. According to Sprague,[20] murmurs, in the main, are transmitted best in the direction of the current. This is due to the fact that the eddies are propagated and released in this direction, but more to the fact that the point of impact of the stream upon a solid body must be distal to the obstruction. However, if the murmur is loud enough, it will be transmitted somewhat in all directions by local resonators and direct continuity of solid bodies.

When pulsations are felt in the suprasternal notch, this valuable sign indicates the presence of a dilated and elongated aorta. Stern[21] believes that since the first portion of the aorta is held firmly by the heart, which is anchored by the pericardial sac, and the descending portion is attached to the spine, any lengthening must be accompanied by a bulging upward of the

arch. This elevation pushes up the origin of the vessels that arise from the arch and causes them to bend and buckle. This buckling places a portion of the artery (especially the innominate or right carotid) into the suprasternal notch where it can be felt and at times seen. The impulse under these circumstances comes chiefly from the right and may be mistaken for an aneurysm of these vessels. If the finger is inserted deeply into the suprasternal notch, the aorta itself can be felt as a horizontal pulsating vessel and a diagnosis of an elongated and dilated aorta is easily made. The dilated aorta may cause pulsation in the second or third right or left intercostal spaces which is often mistaken for an aneurysm.

Increased retromanubrial dullness is valuable as a sign only when the aortitis is far advanced and there is moderate or marked widening of the aorta. According to Leaman,[22] if the aorta is inspected in the cadaver, it will be seen to arch in a direction away from the chest wall. In addition, the vessels at the base of the heart are surrounded by lung tissue. Therefore, it is difficult to indicate the diameters of the aorta with any degree of accuracy by percussion over the anterior chest wall. We believe that other conditions such as a deformed anterior chest wall, a thickened chest wall, and emphysema may interfere with accurate percussion in spite of the size of the aorta.

The question of the association of hypertension with cardiovascular syphilis has been a controversial one. Moore, Danglade, and Reisinger [23] studied 105 patients with uncomplicated aortitis who came to necropsy and found that hypertension was an infrequent accompaniment of this condition. Horine and Weiss [24] studied 666 patients with essential hypertension and a control group of 2000 non-hypertensive patients and concluded that syphilis was practically the same in both groups and that, therefore, it cannot have any etiological bearing on hypertension. We believe that our study was more representative because both the group with cardiovascular syphilis and the control group were cases of proved syphilis. On the other hand, Scherf and Boyd [5] state that about 50 per cent of the cases of aortitis have an increased blood pressure (over 150 mm. Hg) which affects the systolic as well as the diastolic pressures. Nothing is known about the cause of this hypertension, and they believe that perhaps factors other than an extension of the inflammatory process to the depressor nerve in the aortic wall are responsible. From our studies it is obvious that hypertension is a common finding in syphilitic aortitis and can be used as a diagnostic aid because the very frequent combination of these two conditions makes it obligatory to consider the possibility of aortitis in every hypertensive patient, especially when the hereditary factor in hypertension can be ruled out from the family history.

Another disputable question has been that of the rôle of hypertension in causing the characteristic aortic second sound. Gager [25] believes that a drum-like or booming quality of the aortic second sound is the result of hypertension. On the other hand, Carter and Baker [16] believe that accentuation of the aortic second sound indicates high pressure levels, whereas a

change in quality means structural alteration in the cusps, ring, or vessel. According to Best and Taylor,[26] the second aortic sound results from the vibrations set up in the blood column and arterial wall as the aortic valve is placed under tension following its closure. The intensity of the second aortic sound is increased by an elevation in the systemic pressure. The condition associated with intensification of the second aortic sound is hypertensive disease which raises the aortic pressure. We believe that hypertension can cause a change in the character of the second sound at the aortic area in addition to accentuation, only when advanced aortic sclerosis is associated with it. Therefore, in the age group of 40 years or older one is unable to differentiate aortitis from aortic sclerosis, with or without the presence of hypertension. Hypertension causes accentuation of the second aortic sound; aortitis and aortic sclerosis change the character of the second aortic sound.

Although this paper deals primarily with the physical diagnosis of uncomplicated syphilitic aortitis, we cannot help but make a few observations on the use of fluoroscopy and roentgenography. It is generally agreed that the use of these instrumental methods requires experience and judgment. There has been much discussion in the literature concerning the value of fluoroscopy and teleoroentgenography in detecting early uncomplicated syphilitic aortitis. Kemp and Cochems [27] conclude from their studies of 1000 unselected syphilitics with those of 600 unselected non-syphilitics, that there is no evidence that the diagnosis of uncomplicated syphilitic aortitis can be made by teleoroentgenography alone; fluoroscopy and careful clinical evaluation of symptoms and physical signs are essential. Blitch, Morgan, and Hillstrom [28] were unable to find roentgenographic and fluoroscopic evidence of syphilitic aortitis among 30 patients with syphilis of 12 years' duration. Padget and Moore,[29] in a critical review of the literature on the roentgenographic diagnosis of uncomplicated syphilitic aortitis, state that commonly used teleoroentgenographic studies were valueless, that the left anterior oblique position might hold some promise, and that fluoroscopic examination in the hands of a competent observer may have some value. Maynard [15] does not place reliance on teleoroentgenography and measurements of the vascular pedicle alone but on careful clinical, fluoroscopic, and orthodiagraphic studies in addition.

In our corroborative studies of the physical diagnosis of uncomplicated aortitis by means of fluoroscopy and roentgenography, we did not use any measurements but depended primarily on our experience in evaluating dilatation of the aorta. We considered age, sex, size, body build, and chest deformities in our evaluation, and found that the left anterior oblique view was most valuable for the study of the aorta.

It will be noted from our results that uncomplicated syphilitic aortitis is a truly asymptomatic disease. Opinions differ on this statement. Cole and Usilton [3] include in their criteria for the diagnosis of uncomplicated aortitis a history of circulatory embarrassment, progressive cardiac failure, substernal pain, and paroxysmal dyspnea. Maynard [15] has aptly shown

that from his experience these findings are the result of the complications of aortitis. Wilson [30] studied 211 patients with syphilitic aortitis and demonstrated that every case with symptoms referable to the heart had one of the complications of cardiovascular syphilis or some coexisting disease. He concluded that uncomplicated syphilitic aortitis was an asymptomatic disease and that no criteria dependent upon symptoms were reliable in making an early diagnosis.

Most text books and periodicals claim that cardiovascular syphilis is rare among congenital syphilitics. Our results show that 16 per cent of the congenital cases studied presented clinical evidence of aortitis, and all but one showed some degree of aortic dilatation by fluoroscopy and roentgenography. Kurtz and Eyster [31] studied a small series of 12 cases of congenital syphilis with special reference to the fluoroscopic findings in the heart and aorta. The fluoroscopic evidence of aortitis was found in 36.4 per cent of the cases. They based the diagnosis of the presence of aortitis and the degree (slight, moderate, or marked) upon the shape of the ascending aorta—sagging of the ascending aorta to the right with pulsations visible to the right of the sternum, and the density of the descending aorta. Cardiovascular syphilis is rare in infants with congenital syphilis, but in older children and adults who have received inadequate or no treatment there is no reason why this condition should not be recognized more frequently, especially since it has been demonstrated that central nervous system syphilis is just as frequent in congenital syphilis as in the acquired type. Kurtz [32] reports a series of 20 cases with congenital syphilis studied by fluoroscopy and orthodiascopy. There were seven males and 13 females ranging from nine to 47 years of age. Most of these had received no antisyphilitic therapy up to the time of admission. The aorta was dilated slightly in seven cases, moderately in one, and appeared normal in the remaining 12. He makes no mention of the physical findings in the eight cases (40 per cent) of aortitis.

All the congenital syphilitics studied were proved cases, and the criteria for the clinical diagnosis of syphilitic aortitis were the same as in the acquired type. Yampolsky and Powel [33] report a case of proved congenital syphilis in a nine year old child in whom the diagnosis of aortitis of syphilitic origin was made pathologically. McDonald [34] reports 11 cases of syphilitic aortitis occurring in patients up to 30 years of age with congenital syphilis. The diagnosis was made post mortem. These cases were not followed for any period of time before death but were admitted to the hospital with various acute conditions. Some degree of coronary ostial stenosis was present in practically all the cases.

## Treatment

No attempt will be made to present an exhaustive treatise on the treatment of cardiovascular syphilis but rather to point out the dangers and discuss the routine of such treatment.

It should be remembered that in treating patients with cardiovascular syphilis there is a greater tendency to react unfavorably to medication, and the reaction is likely to be more severe and dangerous than in a patient who has no cardiovascular involvement.

In outlining a program for the treatment of cardiovascular syphilis, Moore [35] considers the possibility of reactions and plans his treatment with the idea of prevention.

During treatment or immediately thereafter the patient may suddenly show pallor followed by marked tachycardia, cold perspiration, failing pulse, and occasionally death within a few minutes. This reaction is likely to occur when the drug used is old arsphenamine, and it may be due either to the greater toxic effect of the drug or possibly to the greater volume of fluid necessary for its administration. By the use of milder drugs less toxic in nature, and in smaller easily controlled doses, this reaction can to a certain extent be avoided.

The very common mild nausea and vomiting that occur in certain types of patients after treatment present a danger in cardiovascular syphilis and should be prevented. Here also smaller doses of less toxic drugs are of value in preventing any serious damage to the myocardium.

A complication associated with the treatment of cardiovascular syphilis is the so-called therapeutic paradox. Here we have an apparently healthy patient with a well compensated heart suddenly developing congestive heart failure after a course or two of antisyphilitic therapy. This is explained by the too rapid healing of the inflammatory tissue and its replacement by scar tissue, with the inflammatory process subsiding but the patient in a poorer condition than before treatment was started. This reaction can be avoided by giving a preliminary course of bismuth and iodides followed by small doses of mildly acting arsenicals such as neoarsphenamine or mapharsen.

The Herxheimer reaction which may occur a few hours after the first injection of an arsenical, must be borne in mind and carefully avoided. The local edema in the aorta that comes on suddenly may be particularly dangerous if it occurs at the mouth of a coronary artery, where it may lead to immediate death. This reaction can be avoided by starting with a course of bismuth and iodides followed by very minute doses of the arsenicals.

All patients with cardiovascular syphilis should be started with a preparatory course of bismuth [36] and iodides, before any arsenical therapy is attempted. This course should consist of at least 10 to 12 intramuscular injections of bismuth subsalicylate in oil (0.1–0.2 gm.) at weekly intervals followed by a similar course of neoarsphenamine (0.1 gm.) or mapharsen (0.01 gm.) and gradually increasing the dosage. With the exception of cases with uncomplicated syphilitic aortitis, the dosage should not exceed 0.3 gm. of neoarsphenamine or 0.03 gm. of mapharsen in any cardiac condition. Old arsphenamine should never be used in the treatment of cardiovascular syphilis.

The course of treatment should be continuous without any rest period.

and if there are no reactions or contraindications, it should be continued for at least two years. As a rule the best procedure is to alternate the treatment so that 10 to 12 injections of bismuth are followed by 10 to 12 injections of an arsenical, and repeated until treatment is discontinued. Although the serological reaction may be checked during this period of treatment, this should have no bearing on the length and type of treatment. At the termination of this regime of treatment, if sufficiently improved the patient is given a rest period of six months and asked to return for a cardiovascular check up, and if necessary for a short course of further treatment.

If the patient has developed aortic insufficiency or aneurysm, treatment must be more conservative. Under these circumstances the preliminary bismuth and iodide therapy is started, but the arsenicals must be used with caution and in many instances their use should be avoided. If the administration of arsenicals is attempted, bismarsen 0.1 gm. intramuscularly at weekly intervals may be tried. The treatment here as in uncomplicated aortitis is prolonged, and a minimum period of two years is required before any rest period is permitted. Under no circumstances should a patient with recognized coronary ostial stenosis be treated with an arsenical. If congestive heart failure for any reason occurs, bismuth and arsenic therapy must be stopped.

Finally, it must be remembered that once the inflammatory process has started and progressed to scarring, treatment will have no effect on the terminal result. For this reason if treatment is late, uncomplicated syphilitic aortitis and its complications will be detected while the treatment is in progress. In other words, treatment cannot prevent a pathologic process that has already started and is far advanced, but will stop it at its inception and prevent the occurrence of such a process.

## Conclusions

The successful clinical diagnosis of uncomplicated syphilitic aortitis depends upon the alertness and the ability of the clinician to recognize this condition as well as upon the extent and distribution of the pathologic process. That this condition is frequently overlooked can be readily appreciated from the difference between its incidence in pathological and in clinical reports. In our series the incidence of uncomplicated aortitis is 24 per cent (304 cases) whereas in reported pathological studies the average incidence is 70 per cent. According to these figures it means that in 46 per cent of the cases the pathologic process is too minimal to be recognized clinically, or is so distributed that recognition by physical diagnosis is impossible.

The clinician is confronted with the problem of diagnosing uncomplicated aortitis in individuals 40 years of age or younger with a history of syphilis, without any complaints and with a negative serological test; or with a negative history, no complaints, and a negative serological test; or with a negative history, no complaints, and a positive serological test. It has been

generally estimated that about 20 per cent of the cases of syphilis give a negative serological test. It is this group of patients, with or without a history of syphilis, that requires our attention as well as our diagnostic acumen for the recognition of uncomplicated aortitis, because they are usually met too late, at a time when they have already developed the complications of cardiovascular syphilis.

With this problem in mind, we were able to recognize 148 cases of uncomplicated aortitis in the younger age group. In this group the negro race predominated by approximately two to one. The presence of the characteristic second aortic sound in the various areas designated was by itself diagnostic of this condition. We know of no other cardiac disease in young individuals (except premature arteriosclerosis) that can produce this sound. Tachycardia due to hyperthyroidism or other diseases may produce it, but it can be easily recognized and differentiated. We believe that hypertension per se is not a problem in the recognition of the characteristic second sound, because hypertension can only accentuate this sound. A systolic murmur is commonly associated with the characteristic second sound. The presence of a systolic murmur alone at the aortic area indicates organic heart disease. Willius [37] has aptly made the following assertion, and we quote: "A systolic murmur that is confined to the aortic area is almost without exception indicative of disease of the aorta or aortic valves, namely, aortic stenosis, aortic sclerosis, or aortitis." If in a young individual rheumatic heart disease or arteriosclerosis can be ruled out, a systolic murmur means syphilitic aortitis with or without the characteristic second aortic sound. The other points mentioned under our criteria for physical diagnosis are corroborative.

We wish to emphasize that a clinical diagnosis of uncomplicated aortitis can and should be made in the presence of a normal sized aorta, if definite and unmistakable physical signs are present.

The presence of the large percentage of hypertensives among the cases of cardiovascular syphilis was somewhat confusing because we were unable to give a valid reason for this finding. From a statistical standpoint we were not able to prove that it was merely a coincidental finding. We agreed, therefore, with the conclusions of Scherf and Boyd,[5] and considered hypertension a diagnostic aid.

We believe that uncomplicated aortitis is not an infrequent finding in congenital syphilis, and that if larger series are studied carefully, our results will be corroborated.

The life expectancy of patients who receive early and adequate treatment with uncomplicated syphilitic aortitis is a normal lifetime, whereas with patients who show complicated cardiovascular syphilis, it ranges from about one to 10 years.

## Summary

Of 1270 cases of proved syphilis studied, 24 per cent were diagnosed clinically as uncomplicated aortitis, and 30.7 per cent as cardiovascular

syphilis as a whole. Of the latter group, 78 per cent were cases of uncomplicated aortitis. The proportion of males to females was approximately two to one, and that of the white to the negro race approximately the same.

The criteria for the physical diagnosis of uncomplicated aortitis are presented and discussed, and are found of value in patients 40 years of age or younger. It is more common in the negro than in the white race in this age group.

The high percentage (47.4 per cent) of hypertension among the cases of cardiovascular syphilis studied is not purely coincidental. No valid reason is advanced for its presence.

Uncomplicated aortitis is more common among congenital syphilitics than has been reported heretofore.

Of 128 cases of cardiovascular syphilis that remembered the chancre, uncomplicated aortitis was diagnosed in 38 cases within 10 years after the primary infection.

Uncomplicated aortitis is a symptomless disease. Hints on physical diagnosis are discussed.

Neurosyphilis was present in 26.6 per cent of the cases of cardiovascular syphilis.

Fluoroscopy and roentgenography are of value in corroborating the clinical diagnosis. Uncomplicated aortitis can be diagnosed clinically in a normal sized aorta.

An outline of treatment is presented.

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# LIPID METABOLISM IN RELATION TO XANTHOMA DIABETICORUM WITH A RECOMMENDATION FOR A NEW NOMENCLATURE *

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FOR a clearer understanding of this paper it is thought advisable to give a review of the present conception of fat metabolism with special reference to fat digestion or absorption and some of the essential data on lipids as related to lipid diseases in general and xanthoma diabeticorum in particular. The terms lipid, lipin and lipoid as used today are synonymous, and include the triglycerides of the fatty acids, cholesterol and cholesterol esters, the phospholipins or phosphatides, the cerebrosides, lipochromes and other fat-containing pigments, such as lipofuscin.

## FAT METABOLISM

It is now the generally accepted view that hydrolysis of the neutral fat of food into its component fatty acids and glycerine is a necessary prerequisite to its absorption. This hydrolysis or splitting of the neutral fat takes place in the small intestine through the actions of the lipase of the intestinal juice —succus entericus—and the pancreatic lipase, steapsin. A certain proportion of the fatty acids, depending upon the reaction of the intestinal contents, form soaps with carbonate and bicarbonate of sodium of the intestinal juices. These soaps, through their property of lowering the surface tension, break up the fat into smaller globules thus forming a finer emulsion of fat with the intestinal juices and thereby increasing the total surface area of the fat exposed to enzyme action.

The bile, aided by cholesterol, plays an essential rôle in the digestion of fat. The bile salts, glycocholate and taurocholate of sodium, help in the saponification of fats. The bile acids dissolve the fatty acids which result from the cleavage of the neutral fat and which are insoluble in the intestinal juices. The bile acids, like the soaps and the fatty acids which are held in solution by the bile acids, likewise have the property of lowering the surface tension of the intestinal juices. They thus further the process of emulsification and increase enormously the surface area of fat exposed to the action of pancreatic lipase. The latter is also specifically activated through the cholic acid radical of the bile salts.

The previously accepted theory proposed by Pflüger [1] that fatty acids are absorbed in the form of soaps according to Best and Taylor [2] is "untenable, for soaps which might be formed could not be held in solution in the acid

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fluid of the intestines." Verzar [3] and his colleagues believe that bile acids through hydrotropic action form a complex with the fatty acids (1 molecule of fatty acid to 3 of bile acid) which is soluble and stable in the slightly acid intestinal juices and which diffuses readily into the epithelial cells of the intestinal mucosa. This bile acid-fatty acid complex breaks down into its components after passing the epithelial boundary. The released fatty acids then recombine immediately with the glycerine which has likewise diffused into the cell from the intestinal lumen, and the bile salt is returned through the portal blood stream to the liver. Verzar furnished experimental evidence that as an essential step in the resynthesis of neutral fat in the intestinal mucosa there is an intermediate stage in which phosphorylation of the fatty acid, the introduction of the PO group, occurs with the formation of a specific phospholipid. This observer believes that the adrenal cortex plays an essential rôle in the process of phosphorylation.

The splitting and the resynthesis of the fat in the intestinal mucosa soon after its absorption from the intestinal lumen allow a regrouping of the fatty acid molecules with the formation of a new lipid which is characteristic of each animal species. Bloor [4] has shown that chemical properties of fats are greatly changed in digestion. When an animal is fed with a fat having a high melting point a fat with a lower melting point is recovered in the thoracic lymph, and vice versa. The intestine thus possesses the power to modify the composition of fat during absorption. The new compounds of neutral fats and phospholipids are discharged in a finely emulsified form into the central lymph spaces (lacteals) of the intestinal villi, where the fat appears as a milk-white emulsion called chyle. By rhythmical contractions of the lacteals, the chyle is propelled along into the lymphatics of the mesentery to the receptaculum chyli by way of the left thoracic duct. It then enters the blood stream at the junction of the left subclavian and jugular veins. In the blood the absorbed fats are present in finely emulsified droplets termed chylomicrons.

The blood fat is transported to the tissues, liver and depots for fat. The latter are located mainly under the skin in the superficial fascia or panniculus adiposus, omentum, retroperitoneal regions and interstitial tissue of all organs except in the brain. The fats in the tissues, liver and depots differ in their composition. The storage depots for fat contain almost entirely the triglycerides of the fatty acids which are relatively resistant to oxidation. The fat in the liver is similar in composition to that found in the tissues when active metabolism is not in process and contains much potential energy. During active metabolism the liver fat occupies an intermediary position and is sent to the tissues for utilization. The liver thus seems to act as a storage depot for fat which is ready to be used.

Raab [5] reported a reduction of fat in the blood and tissue and its accumulation in the liver of mammals following pituitrin administration. From this and other experiments he concluded that there is in the anterior and posterior lobes of the pituitary gland, tuber cinereum and walls of the third

ventricle a lipoid influencing hormone which he called lipoitrin and which promotes the absorption and disposal of the blood fat by the liver. Experiments by Bailey and Bremer [6] produced obesity in dogs by a small puncture confined to the hypothalamus in the region of the tuber cinereum. This would point to the hypothalamus rather than the posterior lobe as a factor in the control of fat metabolism.

Schoenheimer and Rittenberg,[7] by feeding mice with fatty acids "earmarked" with deuterium, were able to demonstrate the desaturation of fatty acids in the body. Deuterium is the heavy isotope of hydrogen which can be made to replace ordinary hydrogen in compounds. The concentration of deuterium may be determined accurately in the tissues and the substances isolated from the tissues. With these fatty acid-deuterium compounds they were likewise able to prove that the largest part of the fat in the diet, even when present in small amounts, is first deposited in the depots for fat before it is utilized. The preparation of the fat in the depots for use in the organism may be accomplished easily or with difficulty. In the latter case, it is taken up very slowly and prepared for use very slowly. This shows the advisability of controlling the weight loss of obese patients, so that they do not lose it too rapidly.[8]

The following lipids are found in the serum: Neutral fat, lecithin, cephalin, sphingomyelin, cholesterol and cholesterol esters. The cerebrosides, also called glycolipids or galactolipids, consist of kerasin, phrenosin, nervone and hydroxynervone and are found chiefly in the nervous tissues and in small amounts only in other organs and in the serum. The neutral fats consist of the triglycerides of the fatty acids, palmitic, stearic and oleic which predominate in human fat. Lecithin, cephalin and sphingomyelin comprise the phospholipid group. Lecithin and cephalin are monaminophosphatides in which the ratio of nitrogen to phosphorus is 1 : 1. Sphingomyelin is a diaminophosphatide in which the ratio of nitrogen to phosphorus is 2 : 1. Cholesterol and cholesterol esters and especially sphingomyelin show more constant values in the serum because they depend largely upon the cellular metabolism of organs and tissues and very little upon intestinal absorption.

There is a physiologic increase of neutral fat in the blood plasma after a fatty meal. In an individual at rest one gram of fat per kilogram of body weight is followed by a slow rise in the concentration of blood fat reaching the maximum value in four hours, then rapidly diminishing and returning to the normal level within six to seven hours. In an individual not at rest the rise occurs more rapidly and reaches the maximum within three hours.[9] A permanent hyperlipemia, however, is always the sign of an abnormal metabolic process in the blood. Hyperlipemia is usually recognized by the milky, opaque appearance of the serum; but an increase of fat up to 150 per cent of the normal value may be present without producing a change in the appearance of the serum.[10] Chemical analysis of the serum, therefore, is necessary to determine the presence or absence of hyperlipemia. The

milky appearance of the serum is usually the result of a marked increase in neutral fat and a proportionate increase of lecithin which generally accompanies the neutral fat. An increase in the cholesterol and cholesterol esters does not produce a milky serum. Cholesterol may or may not parallel the increase of neutral fat and lecithin nor are neutral fat and lecithin proportionately elevated with cholesterol.

The milky serum with its extensive increase in neutral fat is characteristic only of secondary xanthomas due to various types of hyperlipemia. In essential xanthomatosis of the hypercholesteremic [11] group the total cholesterol is increased. It is usually accompanied by only a moderate increase of neutral fat, not sufficient to make the serum milky.

The normal figures for serum lipids (Bloor method) as given by the New York Post-Graduate Medical School and Hospital are as follows:

| | |
|---|---|
| Lipids, total | (500–700 mg. per cent) |
| Fatty acids | (200–420 mg. per cent) |
| Lipid P (lipid esters of phosphoric acid, or phospholipins which include lecithin, cephalin and sphingomyelin) | ( 7–14 mg. per cent) |
| Cholesterol, total | (160–230 mg. per cent) |
| Cholesterol esters | (100–150 mg. per cent) |
| Ratio of esters to total | ( 40–60 per cent) |

Partition of phospholipids (according to the method of Thannhauser, Benotti and Reinstein [12]).

| | |
|---|---|
| Lipid phosphorus | ( 8–11 mg. per cent) |
| Total phospholipid (lecithin, cephalin and sphingomyelin) | (200–290 mg. per cent) |
| Sphingomyelin | ( 15–40 mg. per cent) |
| Cephalin | ( 50–140 mg. per cent) |
| Lecithin | ( 50–200 mg. per cent) |

Approximate values for lipoid content of normal skin (epidermis and cutis, excluding the subcutaneous layer) are the following: total lipoids, less than 3 per cent of the wet weight of the tissue (based on immediate analysis of adequately large specimens); total cholesterol, traces to 15 per cent of the total lipoids; and lecithin, traces to 30 per cent of the total lipoids.[13]

The phospholipid values are affected by various hormones. The plasma phospholipids are decreased by insulin whereas they are increased in the liver after repeated injections of thyroid substance. In rapidly growing malignant tumors the phospholipid content of the tumor cells is higher than in benign tumors of the same tissues or in normal tissues.[14]

Lecithins are found in all cells intimately associated with the phenomena of life. They serve in the blood stream as the chief agents for absorption and transportation of fats. Cephalin, which according to Howell [15] is closely related to thromboplastin or thrombokinase, plays an important part in the coagulation of blood.

Cholesterol is a non-saponifiable fat-like body, named cholesterin from the Greek *chole*, bile, and *steros*, solid. It is a monatomic, simple, unsaturated, secondary alcohol belonging to the sterol group, occurring in the human organism free or as esters of palmitic, stearic and oleic acids. Cholesterol is an essential constituent of the body fluids and of all the cells of the

body, the richest supply being in the brain and adrenal cortex. It is synthesized in the body and is absorbed from animal sterols but not to any appreciable extent if at all from plant sterols.[16] Cholesterol occurs in the blood in the free state and as esters. It occurs in the bile as free cholesterol only and mainly in the same form in the brain and in the human blood corpuscles. The concentration of the total cholesterol is normally the same in the plasma as in the whole blood. Bloor and Knudson [16a] found cholesterol esters 33.5 per cent of the total cholesterol in the whole blood and 58 per cent in the plasma, but the ratio may vary in the latter from 40 to 60 per cent. The ratio of free cholesterol to cholesterol esters is 1:1.4. A reversal of this ratio means a decided destruction of the parenchyma of the liver and usually occurs in xanthomatous biliary cirrhosis.[16b]

Cholesterol esters, like the neutral fats, are hydrolized by the intestinal and pancreatic enzymes and are resynthesized in the intestinal mucosa before reaching the lymph stream, by which route they are mainly absorbed, some of it being taken up directly by the blood stream. Rothschild and Felsen [16c] believe that the liver is the regulator of the cholesterol metabolism, maintaining it at a more or less constant level by excreting the free cholesterol only in the bile and intestine. Some of the biliary cholesterol is reabsorbed from the small intestine, another part is destroyed by the colon bacilli (Ottenstein and Nekam [16d]) but the bulk is transformed by hydrogenation * or reduction to coprosterol and with some unchanged cholesterol is eliminated in the feces. Gardner and Kingsborough [16e] state that cholesterol can be found normally in the urine. Rothschild and Felsen [16c] found the cholesterol low in three cases of acute yellow atrophy, reduced in hepatic disorders and as high as 700 mg. per cent in obstructive jaundice. In patients with jaundice, high temperatures and infection the blood cholesterol content was lower than in patients with the same degree of jaundice but with no infection.

Cholesterol or its products with the aid of the other lipids provide the cells with the power of holding large quantities of water without disturbing the osmotic pressure within the cells, without altering their peculiar semifluid consistency and without dissolving. Free cholesterol is an antihemolytic agent forming a weak molecular union with saponaceous substances like digitonin and hemolytic substances as saponin, other glucosides, animal venom and bile. It thus protects the blood corpuscles of the body and neutralizes the toxic action of the hemolyzing substances and lipolytic enzymes which constantly attack and digest the red blood cells. As a constituent of the sebum and waxes of the skin cholesterol protects the epidermal structures. Anemia is produced when the rate of destruction of the red blood cells surpasses the rate of regeneration. In pernicious anemia the

* The terms dehydrogenation and hydrogenation apply respectively to the processes of oxidation and reduction. The accepted theory today is that in the former, dehydrogenases which are present in the cells, take up hydrogen from the saturated fatty acids and deliver it to a hydrogen acceptor and thus unsaturated fatty acids result. In hydrogenation the opposite takes place and the unsaturated fats become saturated by hydrogen.

cholesterol may be reduced 50 per cent or more, and it may be restored by liver therapy.[16f] A rise in cholesterol occurs in conditions involving either physiologic or pathologic cell multiplication. During pregnancy both the total cholesterol and the cholesterol esters are increased.

Among the many other lipid diseases hypercholesteremia also occurs in chronic hemorrhagic nephritis, diabetes and especially in nephrosis.[16g] Barker [16h] has shown that a prolonged diet deficient in protein produces liver damage and a rise in blood cholesterol. Cholesterol, besides its importance as an essential constituent of cells, is of great interest because of its close chemical relationship to the bile acids, vitamin D and the sex hormones.

Jones and Murray [16i] found that the addition of 2 per cent cholesterol increased the cleansing efficiency of the skin 1200 per cent as measured by its effect in removing dirt and keratin. Cholesterol by its ability to absorb 80 per cent of water helps to form a valuable salve in which water soluble drugs may be dissolved and applied.

The cholesterol metabolism is dependent upon thyroid function as shown by the hypercholesterolemia in hypothyroidism and the reverse in hyperthyroidism.

The esterification of the cholesterol takes place in the intestinal mucosa and in the liver as shown by diseases of that organ as well as in obstruction of the biliary tract when there is a rise in free cholesterol and a corresponding decrease in cholesterol esters.

Bloor [16j] analyzed smooth, cardiac and skeletal muscles of various mammals, birds and cold-blooded animals for the cholesterol and phospholipid contents. Smooth muscle was found to have the lowest phospholipid-cholesterol ratio whereas in cardiac and skeletal muscles the ratio was four times that amount. Bloor concluded that "to some extent the cholesterol content may be related to spontaneous activity of smooth and cardiac muscle, and the phospholipids to energy expenditure."

In the tissues each one of the aforementioned lipids except lecithin and cephalin may be pathologically predominant. The terms cholesterosis, cerebrosidosis or sphingomyelinosis are used to designate the specific lipid respectively involved whereas the name fatty degeneration is employed when neutral fat mainly is increased. In xanthomatoses it is the cholesterols that are chiefly accumulated.[17] The diaminophosphatide, sphingomyelin, is the lipid involved in Niemann-Pick's disease (splenohepatomegaly). In this disease an enormous aggregation of sphingomyelin with a slight increase of fat and cholesterol may be found in the histiocytes and reticulum cells of almost all the organs, whereas the amount in the plasma and body fluids is normal. In Gaucher's splenomegaly, possibly as a result of an imbalance or enzymatic disturbance,[18] there is an increased formation or decreased disintegration of the normally existing cerebroside, kerasin, whereas the sphingomyelin content is normal. A large accumulation of kerasin occurs especially in the liver, spleen, bone marrow and lymph nodes.[19]

## Clinical Features

*Xanthoma diabeticorum* occurs as a rule in patients who are middle-aged, overweight and have glycosuria or a high sugar tolerance curve. The lesions, unless they are fibrotic, appear suddenly and regress fairly rapidly without leaving any trace as a result of treatment directed toward the reduction of the hyperlipemia. They occur preponderantly on the elbows, knees, buttocks and in the neighborhood of hair follicles and sebaceous glands. They are also found on other parts of the integument and buccal mucous membrane. The lesions are usually numerous, discrete, confluent or grouped and consist of pinhead to pea-sized, firm, conical or acuminate papules which have a reddish halo indicative of the inflammatory process in diabetes and which are the first to disappear with the improvement in the diabetic state. In the papulo-pustular type of this disease (extracellular cholesterosis of Urbach) the papules or nodules have yellowish solid tops resembling pustules which are frequently covered with fine telangiectatic capillaries.

The subjective symptoms vary from slight itching to tingling sensations or tenderness. Jaundice is never found and the heart is not involved. The serum is milky because of the presence of large amounts of neutral fat.

*Histologic Findings.* It has been emphasized by Ormsby,[20] Thannhauser [21] and others that in xanthoma diabeticorum very few or only occasional foam cells are found and the inflammatory process is more marked, whereas in xanthoma tuberosum and xanthoma disseminatum many foam cells are seen. Histologic sections of the lesions in the case (Wise and Garb [22]) of a colored woman showed on the contrary numerous xanthoma cells. Satenstein [23] stated that a differentiation could not be made histologically between the three aforementioned xanthomatous lesions.

## Differential Diagnosis

*Xanthoma diabeticorum* must be differentiated mainly from xanthoma disseminatum and xanthoma tuberosum. The chief differential points aside from the distinctions in their clinical manifestations are as follows: Xanthoma diabeticorum is not a disease entity but the symptom and the result of hyperlipemia secondary to diabetes. It belongs to the group of eruptive or secondary xanthomas in contradistinction to xanthoma tuberosum and xanthoma disseminatum which are disease entities belonging to the group of primary or essential xanthomatoses and are thought to be due to a disturbance of the intracellular cholesterol metabolism.

*Xanthoma tuberosum* (multiplex) is an idiopathic or essential xanthomatosis of the hypercholesteremic group. The lesions appear insidiously and do not as a rule regress. The growths are nodular, from pinhead to 4 to 7 cm. in diameter, orange or carrot-yellow in color, isolated or in small groups. The surface of the lesions is usually hyperkeratotic. They are commonly found on the extensor surfaces of the elbows, hips and knees and may be of such a size as to impede the movement of these joints. They are

never seen in the axillae or bend of the elbows and knees, which are the areas of predilection of xanthoma disseminatum. They do not occur on the mucous membranes or in the larynx [24] unless they are complicated by a secondary hyperlipemia. There is no glycosuria but jaundice is frequent because of xanthomatous involvement of the liver or biliary passages. Angina pectoris and coronary sclerosis are likewise frequent complications. The serum is not milky because only the cholesterol and cholesterol esters are elevated while the neutral fat is but slightly increased. A cholesterol-free diet may help the general condition but usually has very little effect on the lesions themselves, although Montgomery [25] reported several cases which had undergone involution when a diet low in animal fat was given.

Xanthelasma of the eyelids may occur alone or together with xanthoma tuberosum with or without a lipid disturbance of other organs. A cholesterol content of the blood of over 300 mg. per cent would indicate a systemic lipid disturbance.[25a]

*Xanthoma disseminatum* differs from both xanthoma diabeticorum and xanthoma tuberosum. Like the latter it is also an essential xanthomatosis but of the normocholesteremic group. The lipids including cholesterol are usually within normal limits and the serum, therefore, is not milky. The lesions are widely disseminated and are situated predominantly on the flexor surfaces, on the sides of the neck, within the axillae and flexures of the knees and elbows, but not on the extensor surfaces. They are slightly raised, smooth patches consisting of about pinhead-sized papules arranged in ridges or lines so closely grouped in such areas as the neck or abdomen as to appear confluent, but on stretching of the skin are found to be separated by furrows. The color varies from maroon or chamois in the newer lesions to dark brown in the older ones. In contrast to the eruptive forms the patient is not annoyed because there is no itching or tenderness. These growths frequently involve the mucous membranes of the mouth, pharynx and larynx and may affect any organ of the body. Thannhauser and Magendantz [26] believe that lipoid proteinosis which Urbach and Wiethe described as "lipoidosis cutis et mucosae" [27] is not an independent clinical manifestation but scar tissue formation as a sequel of xanthoma disseminatum. The posterior pituitary gland, hypothalamic region or the area around the third ventricle may be invaded, interfering with the hypophyseal-hypothalamic mechanism and causing diabetes insipidus. Xanthoma disseminatum may simultaneously involve and produce defects in the membranous bones of the skull and cause exophthalmos by granulomatous masses extending forward within the orbit. Thus the triad, diabetes insipidus, exophthalmos and bone defects known as the Hand-Schüller-Christian syndrome may result though each one of the syndrome may occur alone with or without any cutaneous manifestations of disseminated xanthomatosis.

The blood vessels, heart and coronaries are not affected in this lipid disturbance. A diet low in animal fat and cholesterol has no effect on these xanthomatous lesions because the disturbance is considered to be due to a

dysfunction of cholesterol metabolism within the cell, for which no therapy is as yet known. Thyroid medication is not indicated because the blood cholesterol is normal.

## Classification and Comment on Nomenclature

Xanthoma diabeticorum was first described in 1851 by Addison and Gull.[28] Their description of the lesions is so vivid that it is worth quoting: "The eruption somewhat suddenly appeared on the arms. In the course of ten days it had extended over the arms, legs and trunk, both anteriorly and posteriorly, also over the face and into the hair. It consisted of scattered tubercles of various sizes, some being as large as a small pea, together with shining colorless papules. They were most numerous on the outside and the back of the forearm, and especially about the elbows and knees, where they were confluent. Along the inner side of the arms and thighs they were more sparingly present, and entirely absent from the flexures of the larger joints. Besides the compound character produced by the confluence of two or three tubercles, which appeared to be such, as shown by the prominent whitish nodules upon them, some looked as if they were beginning to suppurate and many were not unlike the ordinary molluscum, but when incised with a lancet they were found to consist of firm tissue which on pressure gave out no fluid save blood.

"They were of a yellowish color, mottled with a deepish rose tint and with small capillary veins here and there ramifying over them. They were accompanied with a moderate degree of irritation, hence the apices of many were rubbed and inflamed."

Malcolm Morris[29] in 1883, describing the fourth case, was first to separate the disease as distinct from but related to ordinary xanthoma. Combes and Behrman[30] suggested the name of xanthoma eruptivum because "a study of pathogenesis of the disease makes apparent the inaccuracy of the name xanthoma diabeticorum." I am of the opinion that the name xanthoma eruptivum would be confusing unless it is modified by the type of the lipid disease in question. Thannhauser[31] applies the name of eruptive xanthoma not only to the secondary xanthomas occurring as a result of hyperlipemia but also to the xanthomas occurring in some cases of xanthomatous biliary cirrhosis which belong to the primary essential xanthomatoses of the hypercholesteremic group. He differentiates secondary xanthomas following diabetic hyperlipemia from the rare cases of secondary xanthomas due to hyperlipemia in chronic pancreatitis with or without concomitant hyperglycemia and glycosuria, depending upon whether the cirrhotic changes of the pancreatic tissue also encroach upon and involve the islets of Langerhans. Both these types show a milky serum due to a great increase of neutral fat but differ in their response to insulin. In diabetic hyperlipemia insulin has a specific influence on the diabetes, hyperlipemia and the secondary xanthomas. It will clear up the diabetic state and cause a

resolution of the xanthomatous lesions. In pancreatic hyperlipemia, on the other hand, insulin will have no effect on the hyperlipemia and the secondary xanthomas may persist. It is for this type that the antilipemic hormone, lipocaic of Dragstedt and coworkers, should be tried although the results thus far have not been satisfactory. Histologically in both of these types of secondary xanthomas foam cells are found but usually not in as great numbers (case of Wise and Garb [32] excepted) as in the essential xanthomatoses. The inflammatory reaction is more prominent in the hyperlipemic type. These secondary xanthomas may also occur as a complication of the essential lipidoses and are also a part of the syndromes of Bürger and Grütz (idiopathic, familial hyperlipemia with hepatosplenomegaly and secondary xanthoma), Von Gierke's disease (glycogen storage disease) and hyperlipemia in lipoid nephrosis. The characteristics of the secondary xanthomas whether they occur as a clinical entity in xanthoma diabeticorum, with pancreatic hyperlipemia, in the aforementioned syndromes or as a complication of the essential lipidoses are all alike. That is, they are papular or nodular in type and will or will not respond to insulin and diet depending upon whether the hyperlipemia is due to a disturbance in carbohydrate metabolism or derangement of an internal fat hormone in chronic pancreatitis. When the secondary xanthomas (diabetic) occur as a complication of an essential xanthomatosis the insulin, low fat and low cholesterol diet will cause a regression in the secondary xanthomatous lesions but will have little or no effect on the original lesions of the primary xanthomatosis.

The eruptive variety occurring in some cases of xanthomatous biliary cirrhosis is papulo-pustular in type as a result of extreme hypercholesteremia with very little or no increase in neutral fat. Thannhauser [33] classifies this type as the "second type of eruptive secondary xanthoma occurring in diabetes." He calls it "extracellular cholesterosis." It conforms with the clinical appearance of eruptive xanthoma first described as xanthoma diabeticorum by Addison and Gull in 1851, the description of which has been quoted here verbatim. Although these eruptions may occur in patients with diabetes they are apparently independent of the diabetic condition because the two patients, H. L. and F. L.,[34] with xanthomatous biliary cirrhosis and papulo-pustular type of xanthoma which Thannhauser describes, had normal blood sugars and no glycosuria. Histologically no foam cells are found in this type of eruptive xanthoma but lipid granules which stain orange-red with the Sudan III stain are present. Symptomatically this papulo-pustular type is characterized by severe itching in contrast to the secondary xanthomas following hyperlipemia, which usually are only slightly pruritic but are frequently tender to touch.

This discussion clearly shows that the name xanthoma eruptivum alone is not adequate as it is a general name which includes the papulo-pustular type of xanthomas complicating the primary lipidosis of xanthomatous biliary cirrhosis and the secondary xanthomas due to hyperlipemia, the latter being subdivided into diabetic hyperlipemia and the rarer hyperlipemia occur-

ring with chronic pancreatitis. Excluding those secondary xanthomas that occur as part of the syndromes previously mentioned, only the secondary xanthomas occurring with hyperlipemia due to diabetes or with chronic pancreatitis would have to be qualified thus: Xanthoma eruptivum (diabetic) and xanthoma eruptivum (pancreatic). A reasonable alternative would be to adopt the latter name only and retain the classic name of xanthoma diabeticorum for the secondary xanthomas with diabetic hyperlipemia. The eruptive xanthomas occurring in patients with xanthomatous biliary cirrhosis would be called xanthoma eruptivum (papulo-pustular) or extracellular cholesterosis, whether they occur with diabetes or not, although Thannhauser uses the name extracellular cholesterosis for those cases of papulo-pustular type of eruptive xanthoma occurring in diabetics only.

## Summary

The most essential facts of lipid metabolism have been brought out to facilitate the understanding of the lipidoses and the commentary on the nomenclature of the eruptive xanthomas. Clinical differentiations among xanthoma diabeticorum, xanthoma tuberosum (multiplex) and xanthoma disseminatum have been fully described.

The name xanthoma eruptivum would not be advisable to adopt as it would include several lipid diseases with different clinical characteristics and might tend to cause confusion. The nomenclature of xanthoma eruptivum (diabetic) and xanthoma eruptivum (pancreatic) is herein recommended to differentiate between the xanthomas occurring with diabetic hyperlipemia and the xanthomas resulting from the hyperlipemia with chronic pancreatitis due to disturbance of the internal fat hormone (lipocaic). For convenience it may be advisable to adopt the latter name only and retain the classic name of xanthoma diabeticorum because of the distinctive clinical features of that metabolic disturbance.

The name extracellular cholesterosis or xanthoma eruptivum (papulo-pustular) should be applied to those eruptive xanthomas, diabetic or not, occurring with xanthomatous biliary cirrhosis which are inflammatory, very pruritic and resemble pustules but when incised are found to consist of solid tissue.

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# THE INCIDENCE OF ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS IN RHEUMATIC HEART DISEASE*

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It is well known that the possibility of developing acute or subacute bacterial endocarditis constitutes a decided threat to the patient with rheumatic disease.[1, 2, 3, 4, 5, 6, 7] Fully 20 to 25 per cent of all patients whose hearts have been the site of preëxisting rheumatic activity are said to fall prey to the ravages of infectious endocarditis. Moreover, 90 per cent or more of all bacterial endocarditis is found in hearts that have been previously damaged by the rheumatic infection.[5]

Believing that it might prove profitable to inquire once again into the incidence of superimposed infectious processes in rheumatic heart disease, the necropsy records of patients with evidence of old or recent rheumatic infection of the heart were analyzed, and particular reference was made to (1) sex, (2) age at time of death, and (3) age distribution. Only cases in which the diagnosis has been confirmed at autopsy are included in this series. No special emphasis is placed on the sites of preëxisting valvular lesions, as this phase has been adequately covered elsewhere.[2, 3]

The protocols of two Boston hospitals were reviewed. The period of years covered for each hospital is indicated: (1) The Peter Bent Brigham Hospital, 1913–1940, a general adult hospital which admits extremely few patients under the age of 12 years; and (2) The Infants' and Children's Hospitals, 1917–1939, with rare admissions over the age of 12 years.

The proportion of autopsies with evidence of rheumatic heart disease to the total autopsy population, and the incidence of acute and subacute bacterial endocarditis in these cases, is shown in table 1.

Rheumatic heart disease was present in 5.5 per cent of all postmortem

Table I

| | P.B.B.H. | Child. H. | Totals |
|---|---|---|---|
| Total number autopsies | 4400 | 3900 | 8300 |
| Rheumatic heart disease number | 415 | 37 | 452 |
| Autopsy incidence R.H.D. | 9.40% | 0.95% | 5.40% |
| Bacterial endocarditis number | 109 | 6 | 115 |
| Incidence B.E. in R.H.D. | 26.20% | 16.20% | 25.40% |

Key to abbreviations:

P.B.B.H.: Peter Bent Brigham Hospital.
Child. H.: Infants' and Children's Hospitals.
R.H.D.: Rheumatic heart disease.
B.E.: Bacterial endocarditis (acute and subacute).

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examinations, or one in every 18 cases (452 out of 8300). This incidence was 10 times as high at the Peter Bent Brigham Hospital (9.4 per cent) as at the Children's Hospital (0.95 per cent), as might be expected from the known high incidence of rheumatic carditis in young adults.

Acute or subacute bacterial endocarditis was present in 25 per cent of these rheumatic hearts, or one in every four cases (115 out of 452). The greater frequency of this complication in adult patients (P.B.B.H. 1:4 to Children's Hosp. 1:6) is most likely due to the increasing hazard to them of superimposed infectious processes.

TABLE II

| Age Period | Rheumatic Heart Disease | | | | Bacterial Endocarditis in R.H.D. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number of Cases | | | % of Total R.H.D. Cases | Number of Cases | | | % of Total B.E. Cases | % B.E. in Total R.H.D. Deaths |
| | Male | Female | Total | | Male | Female | Total | | |
| Below 10 years | 17 | 12 | 29 | 6.4% | 2 | 2 | 4 | 3.5% | 13.8% |
| 10–19 years | 23 | 29 | 52 | 11.5% | 5 | 8 | 13 | 11.3% | 25.0% |
| 20–29 years | 35 | 33 | 68 | 15.1% | 15 | 13 | 28 | 24.4% | 41.2% |
| 30–39 years | 26 | 37 | 63 | 13.9% | 6 | 9 | 15 | 13.0% | 23.8% |
| 40–49 years | 50 | 40 | 90 | 19.9% | 19 | 7 | 26 | 22.6% | 28.9% |
| 50–59 years | 37 | 35 | 72 | 15.9% | 6 | 15 | 21 | 18.3% | 29.2% |
| 60–69 years | 29 | 25 | 54 | 12.0% | 5 | 0 | 5 | 4.3% | 9.3% |
| 70–79 years | 11 | 10 | 21 | 5.3% | 1 | 1 | 2 | 2.6% | 12.5% |
| 80–89 years | 1 | 2 | 3 | | 0 | 1 | 1 | | |
| Totals | 229 | 223 | 452 | 100.0% | 59 | 56 | 115 | 100.0% | 25.4% |
| Average age at death | 40.6 | 39.8 | 40.2 | | 38.2 | 36.9 | 37.6 | | |

Table 2 represents the combined data from both hospitals investigated. It notes the distribution and incidence of rheumatic heart disease and of acute and subacute bacterial endocarditis by age at time of death, for each sex separately and for both sexes together.

The distribution of males and females was equal in both the total group of 452 cases with rheumatic heart disease and in the 115 instances of bacterial endocarditis. Most deaths with evidence of rheumatic heart disease for both sexes occurred in the fifth decade. The highest incidence of deaths due to bacterial endocarditis occurred between the third and fifth decades among males, and between the second and sixth among females.

When both sexes are considered together, it is noted that the peak decade for deaths with rheumatic heart disease was the fifth. Bacterial endocarditis was not found with equal frequency in all decades. Though it was present even in the very young, and in the very old, it was particularly low under the age of 10 years, and its highest incidence occurred between the ages of 20 and 29. The average age at death was 40 years in the rheumatic series and approximately 37 years for the cases due to bacterial endocarditis.

It is difficult to evaluate properly our data as contrasted with the results

of other investigators due to the non-uniformity and variability of certain aspects of this type of study. First, most reports are based on clinical data of patients, both living and dead, and are not restricted as is this one, to autopsy proved material. Second, our statistics were not limited to cases of primary rheumatic heart disease as the cause of death, but rather included all cases with evidence of rheumatic infection of the heart, whether inactive or active, old or recent. Third, both acute and subacute types of bacterial endocarditis were noted, though the majority were of the subacute form of the disease. Finally, this study was concerned with bacterial endocarditis superimposed only on a rheumatic basis and did not list any case with congenital or syphilitic lesions as the primary defects.

The results of the present study, however, are essentially in accord with the data submitted in similar reports by Davis and Weiss,[3] and Laws and Levine[6] from Boston hospitals, and by Hedley[7] from Philadelphia.

## Summary

The necropsy records of two Boston hospitals were reviewed for the incidence of acute and subacute bacterial endocarditis in rheumatic heart disease, and special reference was made to sex, age at time of death, and age distribution.

Five and one half per cent of all postmortem examinations revealed rheumatic heart disease and 25 per cent of these rheumatic hearts had bacterial endocarditis.

Males and females were equally affected in both the total group with rheumatic heart disease and in that with bacterial endocarditis. The average age at death was 40 years for the former group and 37 years for the latter.

The frequency of bacterial endocarditis among 578 cases of rheumatic heart disease was not the same for the different decades. It was particularly low under the age of 10 and was highest between the ages of 20 and 29.

I should like to express my appreciation to Drs. Samuel A. Levine, Soma Weiss, and Sidney Farber for their helpful suggestions, and to the Pathology Department of the Infants' and Children's Hospitals for permission to review its records.

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# CONCERNING THE INFECTIVITY OF SALIVA IN HUMAN RABIES *

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The infectiousness of saliva in rabid animals was demonstrated experimentally by Zinke, Gruner, Salm, Berendt and others in the early part of the last century. Despite the fact, however, that excessive salivation is a common feature of paralytic rabies in man, only few reports are available in the literature concerning the experimental demonstration of virus in the saliva in human rabies. Pasteur, Chamberland and Roux [1] and Raynaud and Lannelongue [2] were perhaps the first investigators to demonstrate virus in the saliva of infected human beings. More recently Palawandow and Serebrennaja [3] demonstrated the presence of the virus in the saliva of one patient with rabies by intramuscular injection into guinea pigs. At a later date [4] these investigators obtained similar results with the saliva from five additional cases of human rabies. Pawan [5] tested the saliva of six persons with symptoms of paralytic rabies. Swabs moistened with saliva were rubbed into the scarified abdominal wall of seven rabbits, all of which became paralyzed and Negri bodies were demonstrated in the respective brains. By a similar method, virus was demonstrated in the saliva of infected bovines, horses and vampire bats. On the other hand the virus may be absent in some cases, as shown recently by Sabin and Ruchman [6] who failed to demonstrate virus in the saliva of a 55 year old man who died of rabies.

The virus in human beings has been also isolated from parotid, sublingual and submaxillary glands by Pasteur, Chamberland and Roux,[7] Bardach,[8] Pace,[9] and more recently by Leach and Johnson.[10, 11]

Though Kraus, Gerlach and Schweinburg [12] and Koch [13] have pointed out that no cases of rabies have been known to result from the bite of a rabid human being, Koch refers to two cases on record of the direct transmission of the disease from one human being to another; in one instance infection took place during coitus and in the other rabies developed after a bite.

This study began on December 24, 1941, when a seven year old girl was bitten on the right leg by a stray dog. After immediate local treatment of the superficial puncture wound, Pasteur treatment was instituted. Two days later (December 26, 1941), 12 additional persons were attacked by the same dog. A laboratory examination of the brain of this animal, which was shot by the police, revealed numerous Negri bodies in the Cornu ammonis. Eleven of the 13 persons bitten by this rabid dog all received local treatment at the City Hospital followed by the Pasteur treatment, but the remaining two

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could not be located. Of the 13 individuals exposed, three died; two of these had received Pasteur treatment and one refused such treatment. Epidemiological data are presented in table 1 and a summary of the case histories of the three persons who died follows:

TABLE I

Epidemiological Information Concerning Persons Bitten by Rabid Dog

| Name | Age Sex Color | Location of Bite*† | Character of Wound | Pasteur Treatment No. of Injections | Deaths Incubation Period (days) |
|---|---|---|---|---|---|
| L. Ja. | 25FW | Face Eyelid | Superficial puncture, lacerated, multiple | 15 | |
| E. De. | 18MW | Right Hand | Puncture | 10 | |
| J. Yo. | 30MC | Head | Deep, lacerated, multiple | 12 | |
| J. Al. | 7FW | Right Leg | Superficial puncture | 11 | |
| G. Ca. | 16MW | Right Arm | Puncture through clothing | 10 | |
| E. To. | 46MW | Right Hand | Deep, lacerated, multiple | 10 | |
| C. Su. | 66MC | Head | Superficial, lacerated | 10 | |
| E. Br. | 23MW | Left Arm | Superficial puncture through clothing | 10 | |
| L. Wa. | 28MC | Head Eyelid | Superficial, lacerated | 15 | |
| H. Co. | 7MC | Head | Deep, lacerated, multiple | 12 | 17 |
| C. Va. | 33MC | Head, face, lip | Deep, lacerated, multiple | 11 | 22 |
| J. Ha. | 24MC | Lips | Deep, lacerated | None | 40 |
| L. Wa. | 40FC | Right Index Finger | Deep, puncture | None | |

* All persons except J. Al. exposed on December 26, 1941; J. Al. exposed on December 24, 1941.

† All persons received local treatment shortly after exposure; wounds were cauterized with phenol.

Case H. Co., a colored boy, seven years of age, was admitted to the St. Louis Children's Hospital on January 14, 1942. Deep, lacerated multiple lesions were inflicted about the head by a stray rabid dog on December 26, 1941. The child received local treatment at the Homer G. Phillips Hospital and Pasteur treatment was instituted shortly after exposure. The child was given a complete course of 12 injections of the Harris vaccine. The first symptoms of rabies were noted on January 12, 1942, the seventeenth day after exposure. On the second day of illness, the child complained

of generalized weakness and was confined to bed. The following day the child was hospitalized and the principal symptoms were hyperirritability, apprehension, nervous jerking, visual and auditory disturbances, salivation and difficulty in swallowing. Avertin anesthesia was given soon after the patient was admitted to the hospital. The patient died 24 hours after hospitalization and no autopsy was performed.

Case C. Va., a colored man, 33 years of age, was bitten about the head on December 26, 1941, by the same stray rabid dog. Deep, lacerated, multiple lesions were inflicted on the face and lips. This person was given local treatment at the Homer G. Phillips Hospital and Pasteur treatment was started shortly after exposure. Eleven injections of Harris antirabic vaccine were given and the patient failed to return to the Clinic for the final injection to complete the course of treatment. This person first complained of left-sided weakness and difficulty in swallowing and was admitted to the hospital on January 17, 1942, 22 days after exposure. Among the prominent symptoms were vomiting, delirium, convulsions and salivation. The patient was mentally clear between convulsive seizures. The patient died within 24 hours after hospitalization. Spinal fluid was obtained for study and a specimen of ropy saliva was procured during one of the generalized convulsive seizures. No blood specimen was obtained. The patient died on the twenty-third day after exposure and a complete autopsy was performed. Numerous Negri bodies were seen in smear impressions of the Cornu ammonis.

Case J. Ha., a 24 year old colored man, was attacked by the same rabid dog on December 26, 1941. Deep lacerated wounds were inflicted on the lips. The patient received prompt local treatment at the St. Louis City Hospital, but refused to report to the Health Division for Pasteur treatment. Symptoms first appeared on February 5, 1942, forty days after exposure. The principal symptoms were hyperactivity, salivation, convulsions, photophobia and inability to swallow. Between episodes of hyperactivity, the patient would lie quietly and appear perfectly rational. During a convulsive seizure there was increased salivation and the patient had a wide-eyed stare. There was no paralysis of the extremities. The patient died 48 hours after hospitalization and a complete autopsy was performed soon after death. Numerous Negri bodies were demonstrated in the Cornu ammonis. Brain, olfactory bulbs, and salivary glands were obtained for study. Spinal fluid, blood, feces and saliva were obtained about 10 hours before death. The specimen of saliva was obtained while the patient was under heavy sedation by swabbing out the mouth and throat with absorbent cotton. Unfortunately, no specimen of saliva was obtained during a convulsive seizure.

Since several viruses (poliomyelitis,[14, 15] rabies,[16] measles,[17] influenza[18]) have been found to withstand treatment with anesthesia ether, this bactericidal agent was used to eliminate bacteria from the heavily contaminated saliva prior to intracerebral inoculation into mice. All specimens from case C. Va. were transported to the laboratory and immediately frozen and stored in the dry ice storage cabinet until ready for animal inoculation. The specimen of ropy saliva was triturated without an abrasive and using a minimum of broth. The specimen was centrifuged at 2000 r.p.m. for five minutes and the supernate was then divided into two aliquot portions. One portion was inoculated intracerebrally into six lightly anesthetized Swiss mice. Each mouse received 0.03 c.c. The second portion was treated with 10 per cent ether, shaken thoroughly, and allowed to stand in the refrigerator for two hours. After centrifugation at slow speed, the supernatant liquid below the ether layer was removed for animal inoculation. A portion of the Cornu ammonis was similarly treated and served as control of the efficiency of

the method. Undiluted spinal fluid was also injected intracerebrally into each of six Swiss mice.

The results of these animal inoculations are presented in table 2. It will be seen that 12 days after inoculation of the specimen of saliva into the mice they developed rabies-encephalitis which was identified both by symptomatology and by microscopic examination of the mouse brain.

Examination of the brain of the patient revealed numerous Negri bodies in the Cornu ammonis and presence of virus was demonstrated by animal inoculation. After an incubation period of 11 days in mice the virus was demonstrated also in the ether treated human brain. No virus could be detected in the spinal fluid. All mice were observed for 35 days.

TABLE II

Demonstration of Rabies Virus in Tissues from Two Human Cases

| Material Tested | Case C. Va. | Case J. Ha. |
|---|---|---|
| Saliva | 2T, 2T, 3T, 12+, 14+, 18+ | 1T, 3T, S, S, S, S |
| Ether-treated Saliva | 2T, 12D, 14+, 15+, 15D, S | 2T, S, S, S, S, S, |
| Cornu ammonis | 1T, 8−, 10+, 11+, 14+, 16+ | 11+, 11+, 12+, 13+, 14+, 14+ |
| Ether-treated Cornu ammonis | 11+, 14+, 14+, 14+, 15+, 17+ | NT |
| Spinal fluid | S, S, S, S, S, S | S, S, S, S, S, S |
| Olfactory bulbs | NT | 10+, 11+, 11+, 13+, 14+, 14+ |
| Salivary gland | NT | 1T, 12+, 13+, 14+, S, S |
| Ether-treated Feces | NT | 2T, 3T, S, S, S, S |

Each figure represents one mouse and the day of death.
D = Mouse found devoured; no examination for Negri bodies made.
T = Mouse died from trauma or of unknown complications other than rabies.
S = Mouse survived. No Negri bodies found in brain examined after 35 days.
+ = Negri bodies found on microscopic examination.
− = No Negri bodies found on microscopic examination.
NT = Not tested.

The specimens of saliva, spinal fluid, feces, brain, olfactory bulb and salivary gland from case J. Ha. were transported to the laboratory in a portable dry ice storage cabinet. A small amount of broth was added to the saturated absorbent cotton to facilitate expressing the saliva. The saliva was then treated with ether. The specimen of feces was similarly treated prior to animal inoculation. Cornu ammonis, olfactory bulbs and salivary glands were inoculated into mice without previous treatment with ether. From the results summarized in table 2 it will be seen that although virus was present in the brain, olfactory bulbs and salivary gland, none could be detected in the saliva, spinal fluid or feces.

The brain from each of two mice moribund on the fourteenth day after inoculation with untreated and ether-treated saliva from case C. Va. was pooled and passed to additional mice after sections were removed for microscopic examination. The brains from two mice which died on the tenth day after inoculation were pooled and titrated in mice for virus content. (0.03 c.c. of the $10^{-4}$ dilution killed 50 per cent of the mice after intracerebral inoculation.)

Having established the virulence of the virus recovered from the saliva and passed through two generations in mice, neutralization tests were made using (1) blood serum from case J. Ha., who received no Pasteur treatment; (2) blood serum obtained from an individual (J. Yo.) 20 days after having been bitten and 11 days after the completion of a full course of Pasteur treatment with Harris vaccine; (3) pooled serum from two rabbits hyperimmunized with the strain of rabies fixed virus * used in the preparation of the Harris vaccine; and (4) normal human serum (control). Brains from each of three mice of the third generation were removed aseptically, weighed and ground without abrasive and with sufficient beef infusion broth containing 20 per cent normal horse serum to make a 20 per cent suspension by weight. After centrifugation of the pooled brain suspension for five minutes at 2000 r.p.m., serial decimal dilutions were made in beef infusion broth containing 20 per cent horse serum. Equal parts of serum to be tested and virus suspension were mixed to make a final dilution of $10^{-3}$ of virus. Immediately after each virus serum mixture was thoroughly mixed, 0.03 c.c. was injected intracerebrally into each of 15 Swiss mice. It will be seen from the results presented in table 3 that no specific immune bodies were present in the serum from the individual who died 40 days after exposure. Sabin and Ruchman [6] likewise found no neutralizing antibodies in the serum of an unvaccinated case of human rabies who died 20 days after

TABLE III

Results of Neutralization Tests*

| Serum Tested | Day of Death from Rabies Encephalitis† | | | | | | | | | | | | | | | Per Cent Survivors | Chi Square Value‡ | Neutralization |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| J. Ha. | 1T | 10 | 11D | 11 | 11 | 12 | 12 | 12 | 13+ | 14D | 14 | 14 | 15 | 16 | S | 7.1 | 1.12 | – |
| J. Yo. | 13D | 14 | 14 | S | S | S | S | S | S | S | S | S | S | S | S | 80.0 | 19.1 | + |
| Hyperimmune Rabbit Serum | 14 | 15+ | S | S | S | S | S | S | S | S | S | S | S | S | S | 86.6 | 21.99 | + |
| Normal Human Serum | 2T | 9D | 9 | 10 | 10 | 10 | 11+ | 11+ | 12 | 13 | 13 | 15 | 15 | 15 | 17 | 0 | | |

* Undiluted serum was mixed with approximately 100 M.L.D. of virus.

† Following definite signs of involvement of nervous system.

‡ Statistical significance was determined by the calculation of the value of chi square from a four-fold table.[19]

D = Mouse found devoured.

T = Mouse died from trauma or of unknown complications other than rabies.

S = Mouse survived observation period of 35 days.

+ = Animal died from rabies proved by demonstrating Negri bodies; no symptoms observed preceding death.

Serum from J. Ha. was obtained 39 days after exposure; no Pasteur treatment; patient died of rabies.

Serum from J. Yo was obtained 20 days after exposure and 11 days after completion of Pasteur treatment.

* Kindly supplied by Dr. Downey L. Harris.

exposure. Blood serum from the individual (J. Yo.) who completed the full course of Pasteur treatment, and the rabbit immune serum, contained specific neutralizing antibodies against the virus used in these protection tests. The normal human serum which was used as control contained no neutralizing antibodies for the virus.

## Discussion

Recovery of the virus of rabies from the saliva of a human patient confirms the previous reports that it may be present in these secretions.

Since clinical cases of human rabies require almost constant attendance, the question arose as to danger of transmission of the disease to those caring for such patients. If virus is present in the saliva of rabid patients, it would seem wise to take reasonable precautions to prevent saliva from coming into contact with wounds, abrasions, or mucous membranes of attendants.

It may be noted that the specimen of saliva that contained virus was one obtained during a convulsive seizure at which time salivation was very profuse. Incidentally, it was found to have coagulated in the tube after collection. The saliva giving a negative test for virus was obtained by swab from the mouth. This suggests that only the copious saliva during a convulsion may contain enough virus to be detected by present methods so that reported failures to recover virus may have depended on the character of the specimen used.

Mice inoculated with one of the specimens of untreated and ether-treated saliva developed rabies. That mice inoculated with untreated saliva directly into the brain did not die of bacterial infection was undoubtedly due to the absence of bacteria pathogenic for the mouse in these particular specimens.

In the identification of many viruses, immunologic tests are usually considered necessary. Serum neutralization tests are not often done in rabies because of the existence of characteristic inclusion bodies. However, specific serum tests seemed desirable in this case as a further means of identification, and also, as a means of showing that the infecting virus was immunologically the same as the strain used in the Harris-vaccine for prophylactic inoculations.

## Conclusion

1. The virus of rabies may be present in the saliva of human cases, even if it is not always detectable by present laboratory methods.

2. Precautions should be taken by attendants to avoid contact with saliva of rabies infected patients.

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# PULMONARY TUBERCULOSIS OF THE INSANE*

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Refinements in roentgenological technic making possible the rapid, inexpensive chest survey of large groups have stimulated considerable interest in the old problem of tuberculosis among the insane. The authors have made a primary survey in Southwestern State Hospital and have derived certain impressions from their experience in the subsequent management of the tuberculous patients so segregated. The initial survey has been followed by similar studies of all patients admitted since the original survey. It is felt that those now engaged in this work, or who plan work of a similar character, may be interested in our findings and observations.

## Related Findings by Others

The attention of institutional psychiatrists was first directed to this unique problem by Harrington[1] in a report before the old Medico-Psychological Association in 1900, but only nine papers had appeared in the transactions when Klopp[2] reviewed the literature and presented his comprehensive report in 1927. Then only one-half of the hospitals reporting to Klopp were using roentgen-ray plates for diagnosis. Prior to this report important work had been done by Hamilton[3, 4] in estimating the facilities needed by state hospitals in separately caring for the tuberculous insane, and it was generally accepted that 5 per cent of all the total beds in mental institutions should be set aside for the isolation of tuberculous patients.

During the past 15 years exact diagnostic work has been reported with more frequency.[5, 6, 7, 8] A great many state hospitals are now engaged in a complete recheck of their patient population as regards pulmonary tuberculosis. Our survey in March 1939 was the first of several such conducted in Virginia[9] with the help and assistance of the Virginia State Department of Health. At the time of writing, three other Virginia state hospitals have completed roentgen-ray surveys.

## Incidence and Magnitude

In 1927, on the basis of 106 returns on a questionnaire submitted to 163 state hospitals with reference to their facilities for diagnosis and treatment of pulmonary tuberculosis, Klopp[2] obtained figures reporting an incidence varying from 2.9 per cent in western states to 3.6 per cent in the central

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states. Only 57 of the hospitals reporting used roentgen-ray. As far as we can determine, no effort was made to distinguish active from inactive cases at the time. In 1940 we [9] reported an incidence of 4.19 per cent active cases and 5.81 per cent inactive cases at the Southwestern State Hospital. Ours may be considered a primary survey because no previous comprehensive attempt had been made at this hospital to find and segregate active cases. Our figures are somewhat higher than those reported in surveys by others [8, 10] where some degree of isolation had already been in effect when the roentgen-ray survey was made.

Goldberg,[11] on the basis of Illinois state hospital statistics, estimated the incidence of pulmonary tuberculosis in insane patients to be nearly 10 times that of the general population. He surmised that "mental patients are frequently undernourished because they will not eat, they breathe shallowly, they do not exercise unless forced to do so, and the senile, arteriosclerotic and other organic cases are already at a low ebb of vitality. Here nature provides the tubercular bacilli with a fertile living culture medium." In addition to these factors, the work of Lewis [12] with dementia praecox indicates that this particular psychiatric group is constitutionally susceptible to invasion by tubercle bacilli. McGhie and Brink [5] found 47.83 per cent of their patients with dementia praecox to be tuberculous.

## Diagnosis: Methods of Detection

The extreme difficulty of case finding among the mentally ill was pointed out in our earlier report and has also been mentioned prominently by others.[13] Because this aspect of the problem is so important for those planning surveys, the following points are emphasized:

1. Subjective history is unreliable in mental patients. They do not have insight into such complaints as chills, fever, night sweats, cough and hemoptysis. Family histories are not always available.

2. Physical examination is very often unsatisfactory. Mental patients do not cough on direction in a proper manner nor repeat sounds to demonstrate vocal resonance. In a majority of cases they will not even remain quiet enough for a passive stethoscopic examination of the chest. Leonidoff [13] found 3.5 per cent of active tuberculosis was missed on routine physical examination.

3. Positive laboratory diagnosis is often unsatisfactory because mental patients cannot be made to understand the difference between sputum and saliva. Furthermore, they seldom cough. Our failure to obtain positive sputa even in some of our more advanced cases with cavitation confirms the experience of Bower and Schein,[14] who conclude after a special study of this aspect of diagnosis that "the sedimentation rate is a better index of the tuberculous activity than temperature, pulse or weight records." The use of routine blood sedimentation studies has proved valuable in our experience.

Oral temperature recordings for the purpose of diagnosis of pulmonary tuberculosis are certainly not reliable in mental cases for it is seldom that they will hold a mouth thermometer accurately and they are quite likely to bite or break it.

Routine temperature recordings with mentally ill patients are usually rectal temperatures, and this feature is frequently misunderstood or resisted by these patients in actual practice. It is certainly a far cry from struggling with a resistive patient for the sake of a routine rectal temperature to the simple oral, self-recording routine in vogue in sanatoria where patients are not psychiatric problems.

It may be seen from the foregoing that accurate diagnosis in the mentally ill becomes a roentgenological one. The advocates of fluoroscopy [8] claim their method to be less expensive, more rapid and nearly as accurate as the roentgen-ray plate, whereas the proponents of celluloid plates [5, 9, 10, 13] maintain that although plates are more expensive and time-consuming, they are less susceptible to individual examiner's skill, and, moreover, form a permanent record. Miniature 35 millimeter fluorogram seems to be admirably adapted to survey work. However, the various technics have been carefully studied by Larkey [15] and Mercer,[16] who conclude that the standard 14 by 17 inch celluloid film has not been surpassed in reliability.

Our original survey was made on paper films, a method which possesses the advantage of economy and speed at only a slight sacrifice of diagnostic validity. Questionable and debatable films were later checked with celluloid films. After the first survey, however, all of our studies have been made on 14 by 17 inch celluloid plates and we have continued since the survey to make a routine flat plate of the chest on each new hospital admission (and new employee). It is only by doing this that our survey work could be kept up to date, and it may be stated here that, aside from tuberculosis, many incidental findings in regard to the heart, aorta and bony thorax have been brought to light that were not detected on routine physical examination.

Yet even roentgenological diagnosis presents special problems when dealing with mental patients. Exact centering of the plate, proper posture and position of the subject, the correct phase of respiration, are technical details that must frequently be foregone.

## Management and Treatment

An honest attempt to approximate the treatment conditions in general usage in sanatoria was at first made. We soon learned, however, that the time-honored sheet anchor of tuberculosis, bed rest, is, with few exceptions, impossible to maintain. Sane persons may be reasoned with, coaxed or threatened into staying in bed but psychiatric patients are not usually susceptible to coaxing, may be incapable of rational fear, and are not amenable to firmness. Such refinements as sand bags and voluntary vocal silence are too often impractical in a mental institution. Restraint by force usually

defeats its own ends. A few of our patients do remain in bed, it is true, and all of our cases who have active disease are encouraged to do so, but the majority cannot be kept in bed.

Strangely enough, many of our mentally depressed patients with active tuberculosis, who do not improve on a regimen of bed rest, show a weight gain, increased appetite and general clinical improvement when they are encouraged to get out of bed.

Our experience with artificial pneumothorax has led us to believe that this procedure is of particular importance in the treatment of the tuberculous insane. Here we find ourselves in distinct disagreement with Alexander, who lists insanity as a contraindication to pneumothorax.[17] Before we began the collapse treatment, we were fearful that it would not be applicable to mentally diseased cases, but today we are beginning to realize that pneumothorax has a particular value in selected cases. For example, we have been able to maintain several of our pneumothorax cases throughout manic attacks, thus preserving diseased lungs from the dangers of hyperventilation. Many of our pneumothorax patients are too deteriorated to coöperate with the classical "rest cure" but their diseased lungs are at rest by virtue of the gas compression.

Of course all the active cases are given a higher caloric and vitamin diet than the general hospital population. They are not permitted to do any strenuous work, and occupational therapy is carefully moderated. Even when bed rest is absolutely impossible to maintain, activity is discouraged in those patients who are not showing improvement.

## Results

(a) *Survey of Hospital Patient Population.* On March 24 and 25, 1939, using paper films, 1095 of the 1263 patients at Southwestern State

Table I

Survey Data: Incidence of Tuberculosis

| | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Positive tuberculosis, all stages | 34 | 7.7 | 77 | 13.7 | 131 | 10.4 |
| A. Active | 29 | 4.1 | 24 | 4.3 | 53 | 4.2 |
| 1. Minimal | 9 | 1.3 | 11 | 2.0 | 20 | 1.6 |
| 2. Moderately advanced | 13 | 1.9 | 10 | 1.8 | 23 | 1.8 |
| 3. Far advanced | 7 | 1.0 | 3 | 0.5 | 10 | 0.9 |
| B. Inactive | 25 | 3.6 | 53 | 9.4 | 78 | 6.2 |
| 1. Minimal | 22 | 3.1 | 45 | 8.0 | 67 | 5.3 |
| 2. Moderately advanced | 2 | 0.3 | 7 | 1.2 | 9 | 0.7 |
| 3. Far advanced | 1 | 0.1 | 1 | 0.2 | 2 | 0.2 |
| Non-tuberculous lesions including healed lesions suspicious of tuberculosis, later shown not tuberculosis | 210 | 30.0 | 259 | 46.1 | 469 | 37.1 |
| Entirely negative | 437 | 62.3 | 226 | 40.2 | 663 | 52.5 |
| All patients examined | 701 | 100.0 | 562 | 100.0 | 1263 | 100.0 |

Hospital were roentgen-rayed. The remainder were roentgen-rayed, and poor and debatable films were retaken during the next few weeks. In table 1 the findings of this survey are summarized. The more detailed breakdown of this study is given in table 1 and a briefer tabulation of these findings in table 2.

TABLE II

Summary of Survey Data: Incidence of Tuberculosis
In per cent

| | Male | Female | Total |
|---|---|---|---|
| Positive tuberculosis, active | 4.1 | 4.3 | 4.2 |
| Positive tuberculosis, inactive | 3.6 | 9.4 | 6.2 |
| Non-tuberculous lesions | 30.0 | 46.1 | 37.1 |
| Negative | 62.3 | 40.2 | 52.5 |
| | 100.0 | 100.0 | 100.0 |

(b) Since the completion of the above survey of those patients residing in the hospital we have routinely roentgen-rayed the chests of all newly admitted patients. This amounts to 1181 patients in the three-year period embracing March 25, 1939 to March 24, 1942. In table 3 are given the

TABLE III

Comparison of Initial Roentgen-Ray Survey with Roentgen-Ray of Admissions for Three Consecutive Years

| | Original Survey | | Consecutive Admissions | |
|---|---|---|---|---|
| | No. | % | No. | % |
| All chest films | 1263 | | 1156 | |
| Entirely negative for tuberculosis* | 1132 | 89.6 | 1026 | 88.8 |
| Positive tuberculosis all stages | 131 | 10.4 | 130 | 11.2 |
| a. roentgenologically active | 53 | 4.2 | 44 | 3.8 |
| b. roentgenologically inactive | 78 | 6.2 | 86 | 7.4 |

* Includes other abnormalities, and healed lesions suspicious of tuberculosis, later found not tuberculosis.

comparative findings in these two groups. It will be seen that among the serial admissions having roentgen-ray evidence of tuberculosis 3.8 per cent were roentgenologically active, as compared with 4.2 per cent in the original survey. When the inactive cases were considered the greater percentage of 7.4 occurred among the consecutive admissions as compared with the 6.2 per cent found among those residing in the hospital.

These figures would indicate not only that the incidence of pulmonary tuberculosis is high among the mentally ill who have been in the hospital for a long time but also that the incidence is approximately as high at the time these patients are first admitted to the hospital.

McGhie and Brink [5] feel that the too often necessary overcrowding in many state hospitals contributes to the high incidence of tuberculosis in mental institutions. Bogan and others [6] have suggested that most mental patients contract their illness after admission to a mental hospital. Our findings suggest that although these facts may be true the increased incidence of pulmonary tuberculosis is already a major factor at the time of admission.

(c) *Follow-up Studies.* Of the 53 cases active in March 1939, 11 were dead on September 17, 1941, two of pulmonary tuberculosis, nine of other conditions, in which pulmonary tuberculosis was considered a secondary cause of death. Sixteen of these 53 originally active cases were stationary. Six showed a definite spread and 16 were improved. One had completely cleared and three cases were discharged from the hospital before a recheck could be made, and their status was unknown.

Of the originally inactive cases (March 1939) totalling 136, only 48 were in the hospital at the time we rechecked the chests two and a half years later, the others having died from other causes or left the hospital by furlough or discharge. Of these 48 all were roentgenologically stationary except eight. Two of these eight showed a definite reactivation and were reclassified. Three were improved, the lesions being more compact and healed and three were classified as non-tuberculous lesions.

Because the majority of our active treatment cases (pneumothorax) were still undergoing weekly gas injections, we could not state with accuracy the full and final effects of our artificial collapse therapy. The total number of cases treated by collapse amounted to 18, with no deaths and only two major complications (one massive subcutaneous emphysema and one spontaneous pneumothorax). Over 1180 refills had been given. Five of the 18 cases had been discontinued for various reasons, and of the five the lungs of four appeared to be arrested roentgenologically. One of the reëxpanded lungs showed no improvement.

In nearly every instance patients confined in the tuberculosis building, where extra diet is provided and an attempt at a "rest hour" is made, had gained weight and appeared to be clinically improved.

It must be admitted, however, that the above results would not compare favorably with a group of non-psychotic tuberculosis patients, particularly in view of the fact that nearly half of our active cases were only minimal when first detected. (Minimal 45; moderately advanced 27; far advanced 22.)

Results cannot be measured, however, purely in terms of cases cured, arrested and improved. The advantage of isolation to the non-tuberculous patients and personnel is incalculable. A glance at our figures will show that one out of every 24 routine chest plates has shown up a case of active pulmonary tuberculosis. Certainly the time and expense of making two dozen roentgenograms is justified when by so doing an active case of pulmonary tuberculosis is isolated and given adequate treatment, at the same time protecting patients on other hospital wards.

## Summary and Conclusion

On the basis of our primary survey of a representative state hospital for mental patients, and the figures published for comparable surveys, we believe that the incidence of roentgenological active pulmonary tuberculosis among the insane is at least 4 per cent. We have evidence which tends to suggest that this high incidence bears some relation to mental disease itself and that it is not due to institutionalization. A comparison of the incidence of active pulmonary tuberculosis as shown by roentgen-ray in a cross section survey of the hospital population with a series of new admissions shows the incidence of each to be 4.2 per cent and 3.8 per cent respectively while the incidence of inactive pulmonary tuberculosis is 6.2 per cent and 7.4 per cent respectively. Because of the inability of the large majority of mental patients to coöperate with physical examination or to produce sputum for examination, we are convinced that the only positive and thoroughly accurate method of detecting pulmonary tuberculosis in all types of mental patients is by means of the roentgen-ray, either by fluoroscopy, fluorogram or by standard size celluloid plates, the latter being the method of choice.

In our experience it has not been found possible to treat institutional mental patients having pulmonary tuberculosis by the methods in general use for sane patients with the same degree of success. Furthermore, it is felt that artificial collapse has particular merit.

Tuberculosis in state hospitals is a larger problem than has been generally recognized. It is to be expected that 4 per cent of the patients will have active pulmonary tuberculosis. Unless these patients are found, they constitute a source of contagion to the entire population.

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# COMBINED ELECTROCARDIOGRAPHY, STETHOGRAPHY AND CARDIOSCOPY IN THE EARLY DIAGNOSIS OF HEART DISEASE *

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In the diagnosis of heart disease the mind attaches greatest importance to the phenomena that most strongly affect the senses. A roaring murmur or an irregular pulse thrusts itself upon our attention. Diagnostic signs, however, may be so slight that most careful methods are required for their detection.[1]

A synchronized heart sound tracing and electrocardiogram, as an aid in diagnosis, presents distinct advantages. It enables the examiner to better correlate clinical findings. The procedure is unique in the field of diagnosis. Portable equipment permits the physician, at the bedside, to readily substantiate or correct his clinical impressions. An objective aid, so simple and so easily applied, greatly increases the clinician's diagnostic acumen.

We have shown [2] that combined graphic methods constitute a useful adjunct to the routine examination of applicants for flight training. With the aid of these accessory methods of examination, early, otherwise unrecognized heart disease may be detected. Many organic murmurs are overlooked or ignored in routine examinations. Although approximately 25 per cent of systolic murmurs are of significance, only 10 per cent of these are recorded. Graphic records give objective proof of their existence and are of diagnostic assistance. The cardioscope permits the skilled interpreter instantly to recognize and accurately to classify arrhythmias, heart blocks and tachycardias. In 80 per cent of 10 cases of heart disease in a series of 200 pilots examined the electrocardiogram was essential for diagnosis. A stethogram was essential for diagnosis in 20 per cent of the 10 cases. Combined graphic methods were helpful in 70 per cent of these previously undiscovered cases of heart disease. No simple diagnostic aid gives more valuable assistance.

Rappaport and Sprague [3] found that tones of different frequency but of similar intensity affect the human ear differently. The human ear is a better detector of changes in frequency than of changes in intensity. They conclude that the major advantage of the amplifying stethoscope over the acoustic stethoscope is that it enables one to adjust the intensity to the de-

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sired level and thus eliminate modifying characteristics which otherwise can not be overcome.

Mannheimer [4] states that calibrated stethography promises to become a valuable aid in differentiating organic and functional murmurs. We have found that organic murmurs are apt to be associated with abnormalities in heart sounds as well as in the electrocardiogram. Murmurs associated with diminution, obliteration or abnormal accentuation of heart sounds lead us to suspect organic disease. Heart sounds are seldom obliterated by a functional murmur.

Arenberg [5] reports 200 cases examined clinically and checked by graphic methods. He feels that the stethogram is no more dependable than is the ear for differentiating organic and functional murmurs. He has not observed that the stethogram can detect changes in heart sounds associated with a murmur which otherwise might escape detection. A prolonged rasping murmur, loud in the aortic area and transmitted to the neck, was described as systolic by five competent clinicians, two of whom also described a diastolic murmur in the third left interspace at the edge of the sternum. A stethogram showed a diastolic murmur. The first heart sound was found to be inaudible, the reduplicated and accentuated second sound being superimposed upon the loud diastolic murmur at its very beginning. This is but one example of the critical judgment which a stethogram may add in the timing of murmurs; a typical instance of the importance of marked heart sound distortion in the differentiation of an organic from a functional murmur. We have found it advantageous routinely to record heart sounds and murmurs in all valve areas. The microphone, as well as our ears, may detect these sounds better in one than in another area. Commonly an aortic murmur is better recorded along the left sternal border than in the classic aortic area. Similar observations concern mitral sounds and murmurs. This may explain the difficulty experienced at times in recording clinical murmurs. Although clinical and stethographic findings are closely correlated, we have found many murmurs that have escaped the ear of the examiner.

## Method

We have examined 1108 patients with heart disease. Clinical findings were recorded at the time of examination in all instances. Cardioscopy, for rapid classification, followed by combined electrocardiography and stethography, was employed.

The technic was the same as that previously described (plate 1).[2] With the patient in the recumbent position [6, 7] the three standard (limb) leads were recorded. A simplified method,[8] modified from Roth,[9] was employed for recording chest leads.[10] The left arm electrode was removed and applied to the left chest in the fifth interspace at the midclavicular line, lead wire connections remaining undisturbed. The electrode was held in place by the

left fingers of the patient or an assistant, lightly applied to the overlying folded rubber strap. Lead I and Lead III on the control board were selected in turn, a Lead $CR_4$ and Lead V (inverted $CF_4$) being recorded in succession. We have found these companion leads most practical for routine clinical use. The stethogram of the mitral area was recorded with Lead I of the electrocardiogram; with Lead II, the microphone was placed over the pulmonic area; with Lead III, aortic sounds were recorded; tricuspid sounds were recorded simultaneously with $CR_4$. Both conventional (25 mm.) and fast speed (75 mm. per sec.) records were used to reveal more definitely the graphic details of the various heart sounds.

Our patients varied in age from 2 to 87 years, 1048 being adults. The 1108 cases examined have been classified according to table 1. We carefully correlated clinical and stethographic findings in each instance. Our

TABLE I

Diagnosis in 1108 Patients Studied

| | Rheumatic | Syphilitic | Arterio-sclerotic* | Congenital | Undetermined |
|---|---|---|---|---|---|
| No. of Pts..... | 308 | 117 | 649 | 14 | 20 |

* Including hypertensive heart disease and coronary artery disease.

TABLE II

Criteria for Normal Heart Sounds

| | | |
|---|---|---|
| First Sound: | 5–11 vibrations | duration 0.06 to 0.11 sec. |
| Second Sound: | 3–4 vibrations | duration 0.04 to 0.06 sec. |
| Third Sound: | 1–3 vibrations | —taking place 0.11 to 0.14 sec. after the beginning of the second sound. |
| Systolic Murmurs: | 13–35 vibrations | —or more, up to or through second sound if of long duration; if short 0.02 to 0.03 sec. beyond the first sound. |
| Diastolic Murmurs: | 7–45 vibrations | —when counted with the second sound—duration 0.07 sec. or throughout diastole or occupying any portion thereof. |

criteria for normal heart sounds were those advocated by Orias-Menendez,[11] Wiggers,[12] Boyer, Eckstein and Wiggers,[13] and Pazzanese,[14] summarized in table 2.

In 88 per cent of the cases clinical and graphic findings agree. In 12 per cent the stethogram was essential for diagnosis. Particularly was this true of gallop rhythm and early mitral stenosis or aortic insufficiency. In 390 (35 per cent) of the cases stethograms were helpful in diagnosis, otherwise undetected abnormalities of heart sounds being recorded. In no case was a systolic or diastolic murmur heard that was not satisfactorily recorded. The fact that "the murmurs so often look just as they sound" was striking. Sketches of the sounds as heard clinically, when compared with the stethogram, usually have been in accord.

In 731 (66 per cent) of the cases, the electrocardiogram was of assistance in establishing the diagnosis. The value of chest leads increases

in direct proportion to the age of the patient. Between ages 31 and 41, 20 per cent and between 61 and 87, 47 per cent of chest leads were abnormal. Chest leads were abnormal in 29 per cent, confirmatory in 24 per cent and of diagnostic assistance in 5 per cent of the cases examined.

In 42 per cent of the 102 cases of gallop rhythm the timing of the extra sound was misjudged clinically. Stethography established 37 of these as protodiastolic, 29 as presystolic, seven as systolic, two as summation gallop, and 18 graphs showed a prominent auricular sound often with the associated graphic changes of a coronary occlusion. In nine cases a prominent physiologic third sound was mistaken clinically for a gallop sound. Stethography is the only dependable method for differentiating these extra sounds. It is essential for the accurate diagnosis of gallop rhythm.

Extraneous vibrations, i.e., pulmonary sounds, the râles of emphysema, asthmatic wheezing or whistling râles and breath sounds of the dyspneic patient are easily recognized since they are not synchronous with cardiac activity as simultaneously recorded in the electrocardiogram. The ease with which sounds of cardiac and non-cardiac origin can be distinguished is well illustrated by the case of paroxysmal diaphragmatic flutter recently reported by Goodman.[15]

Routine venous pulse tracings were found unnecessary from a clinical standpoint since the intervals established by our criteria were found to be reliable. Our aim has been to simplify rather than complicate a practical routine procedure. Our graphs were recorded under the usual conditions of the home, office, clinic, or hospital, rather than in a sound-proof studio so rarely available for routine clinical examinations. Since operation of the equipment is independent of an outside electrical source it is available for use in field hospital, aeroplane or rural district.

Screening of the general population for hidden cases of tuberculosis and syphilis has become increasingly popular during recent years. Great strides have been made in the control of these infections. With the aid of the cardioscope similar screening for heart disease can be done. A combined electrocardio-stethogram may or may not be recorded, depending upon abnormal or normal cardioscopic findings.

When instantaneous visualization is used chest leads need not be taken if the findings are normal in the cardioscope. When this equipment is not available or if a trained observer is not present to interpret cardioscopic findings, chest leads should be routinely recorded, since no one can know their value in advance. Whereas the cardioscope may be used to determine these changes, our experience has justified the routine use of the companion chest leads described.

A trained technician and interpreter can examine 120 patients during an eight hour day (plate 1). The number of "positives" would probably exceed those found in other types of public health examinations. Results of routine induction examinations of 310 national guardsmen emphasized the

value of the method in searching for obscure heart disease, particularly of the rheumatic type. In four of the five cases having electrocardio-stethograms serious heart disease was revealed. Other cases might have been detected had routine graphic methods been employed.

To attempt to determine the presence or absence of heart disease by examination in an armory or other unsuitable place is often difficult. Excitement, tachycardia, malingering, or the effects of a farewell debauch may be disturbing factors. Cardioscopy, combined graphic records or both

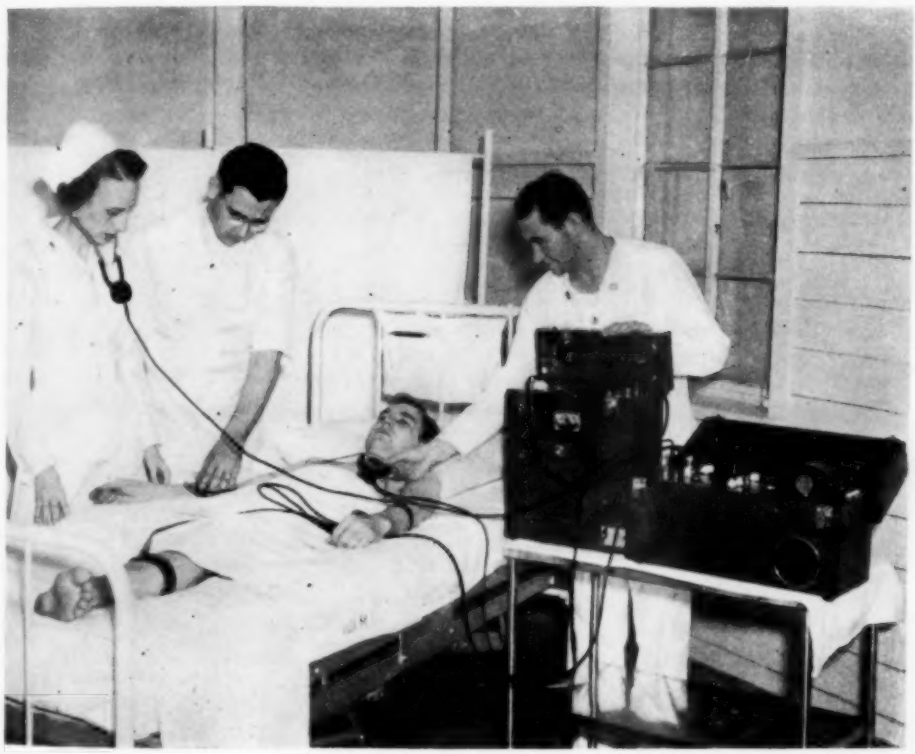

PLATE 1. View of the equipment for taking combined graphic records illustrating how the nurse or physician may listen to the heart sounds and murmurs through the amplifying stethoscope. After the intensity is adjusted properly, it is often possible to hear murmurs missed by the usual acoustic stethoscopic technic. (Photo by Signal Corps, U. S. Army.)

under these circumstances are of distinct advantage in detecting organic heart disease, either active or clinically quiescent but subject to aggravation by active military duty.

It is anticipated that in the near future visualization by means of a double beam cardioscope will give instantly a view of the electrocardiostethogram so that with properly adjusted audiophones, more than one examiner can visualize the sound track synchronized with the electrocardiogram and listen to heart tones and murmurs at the same time.

## Case Reports

*Case 1.* White female, aged 38, on first visit to clinic, June 16, 1936, complained of palpitation with increasingly severe dyspnea of six years' duration and orthopnea of three months' duration, with marked nervousness, loss of weight and appetite. She had been confined to bed for three months at the age of 15 with rheumatic fever. Subsequent attacks of tonsillitis had occurred.

She was poorly nourished. Pulse was 85 per minute and regular. Blood pressure was 110 mm. Hg systolic and 75–70 mm. diastolic. Heart was slightly enlarged to right and left. Apex beat was forceful. A short apical presystolic murmur and a loud aortic systolic murmur were present. Tonsils were large and septic. No other significant findings. A diagnosis of rheumatic mitral disease was made.

Except for extrasystoles, electrocardiograms were repeatedly considered normal. The combined record (figure 1) shows a short faint presystolic murmur in the mitral area, a long loud systolic murmur and a short early diastolic murmur during the first third of diastole in the pulmonic and aortic areas. The aortic second sound is not prominent and is rendered inaudible by the diastolic murmur. This probably explains why a diastolic murmur was not heard.

*Case 2.* Colored female, aged 38, came to the clinic March 7, 1940, and complained of progressive dyspnea on exertion, inability to sleep on her left side and pain in the right shoulder and arm of three weeks' duration.

She was well developed, well nourished and slightly dyspneic. The apex beat was 2 cm. beyond the left midclavicular line in the sixth interspace. The heart was slightly enlarged to the right. A systolic murmur was heard in the mitral and aortic area, the latter being transmitted to the vessels of the neck. Despite the dyspnea and loud systolic murmur she was assured that her trouble was "rheumatism" of the right shoulder; not heart disease. Our clinical opinion, one week later, was that she had an aortic lesion with possible dilatation.

A stethogram (figure 2) revealed a loud crescendo-decrescendo systolic murmur with an accentuated second sound most marked in the aortic area. The electrocardiogram showed an intraventricular block with left axis deviation. The sound record is of particular interest because it shows a prominent auricular sound which could not be heard, a reduplicated first aortic sound which was obscured by the loud murmur and vibrations suggesting an inaudible diastolic murmur in the aortic area. Stenosis and insufficiency of the aortic valve were considered probable. An aortic aneurysm was demonstrated by fluoroscopy.

Had it not been for the dyspnea on exertion, since the systolic murmurs were ignored, the diagnosis might have been missed. The case probably would not have been recognized as heart disease. The diagnosis was established mainly by supplementary aids. We have not seen a functional systolic murmur of this configuration and associated with such changes in heart sounds.

*Case 3.* Colored female, aged 55, first seen on June 2, 1933, complained of hot flashes, headaches, nervousness and shortness of breath of six months' duration.

She was well nourished and not dyspneic but appeared chronically ill. The pupils were fixed to light. The heart was enlarged to the left. Apex beat was visible 3 cm. beyond the left midclavicular line in the sixth interspace. Marked pulsation of the carotids with slight suprasternal pulsation was present. The peripheral arteries were definitely sclerotic. Blood pressure was 210 mm. Hg systolic and 100 mm. diastolic. During the following seven years many clinic physicians consistently recorded a loud systolic murmur in the aortic area transmitted to the vessels of the neck. A diagnosis of aortitis, probably syphilitic, was made. On February 28, 1940, we reëxamined this patient and confirmed the previous findings of a loud systolic murmur. No diastolic murmur was heard.

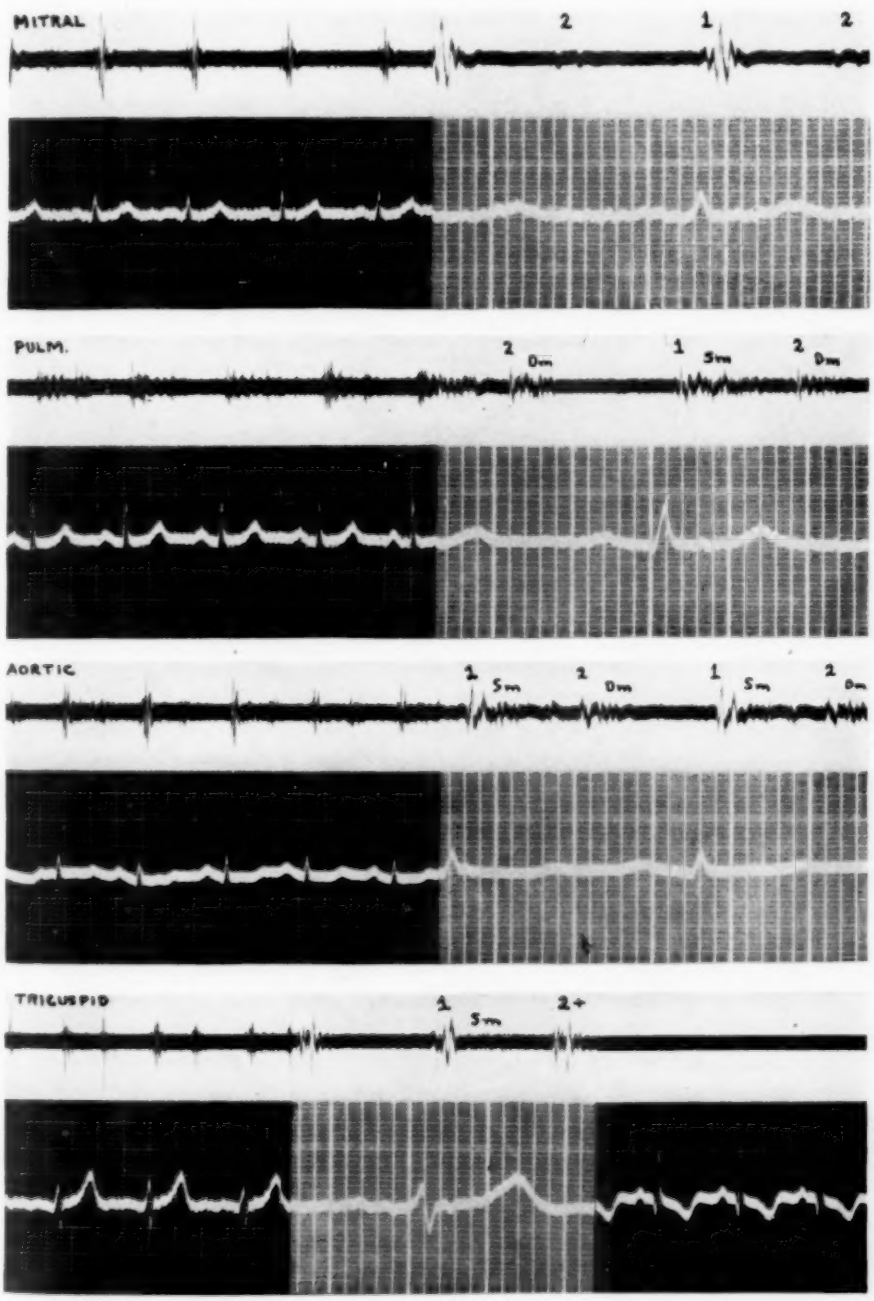


FIG. 1. Case 1.

The stethogram (figure 3) showed a hitherto unrecognized presystolic murmur in the mitral area, a systolic murmur in all areas but most prominent in the aortic area, accentuated aortic and pulmonic second sounds and vibrations suggesting an

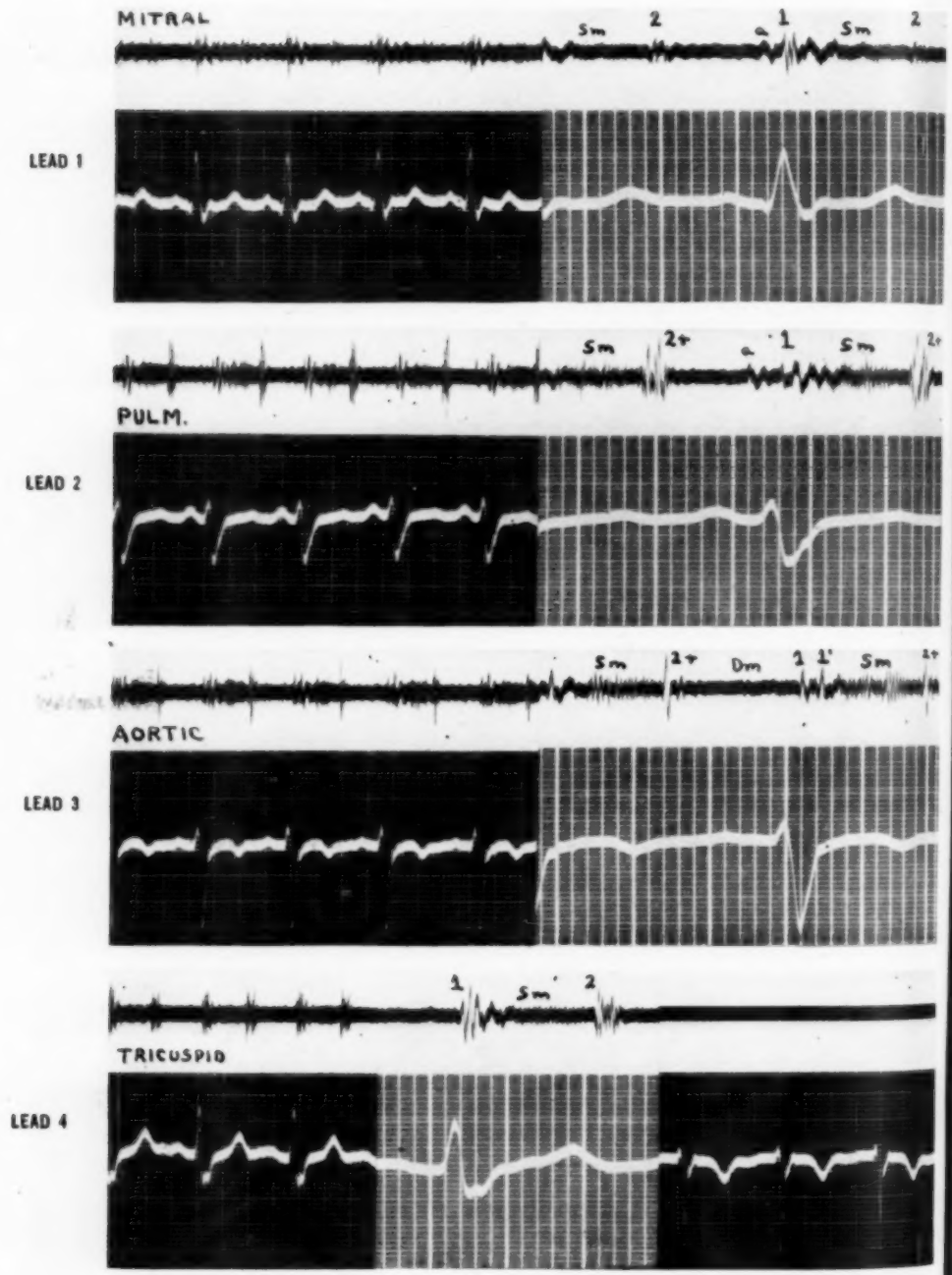


FIG. 2. Case 2.

early diastolic murmur in the aortic area. The aortic systolic murmur was of the decrescendo type which is often described as blowing since it fades away as the second sound approaches. The presystolic mitral murmur, definite in the sound tracing,

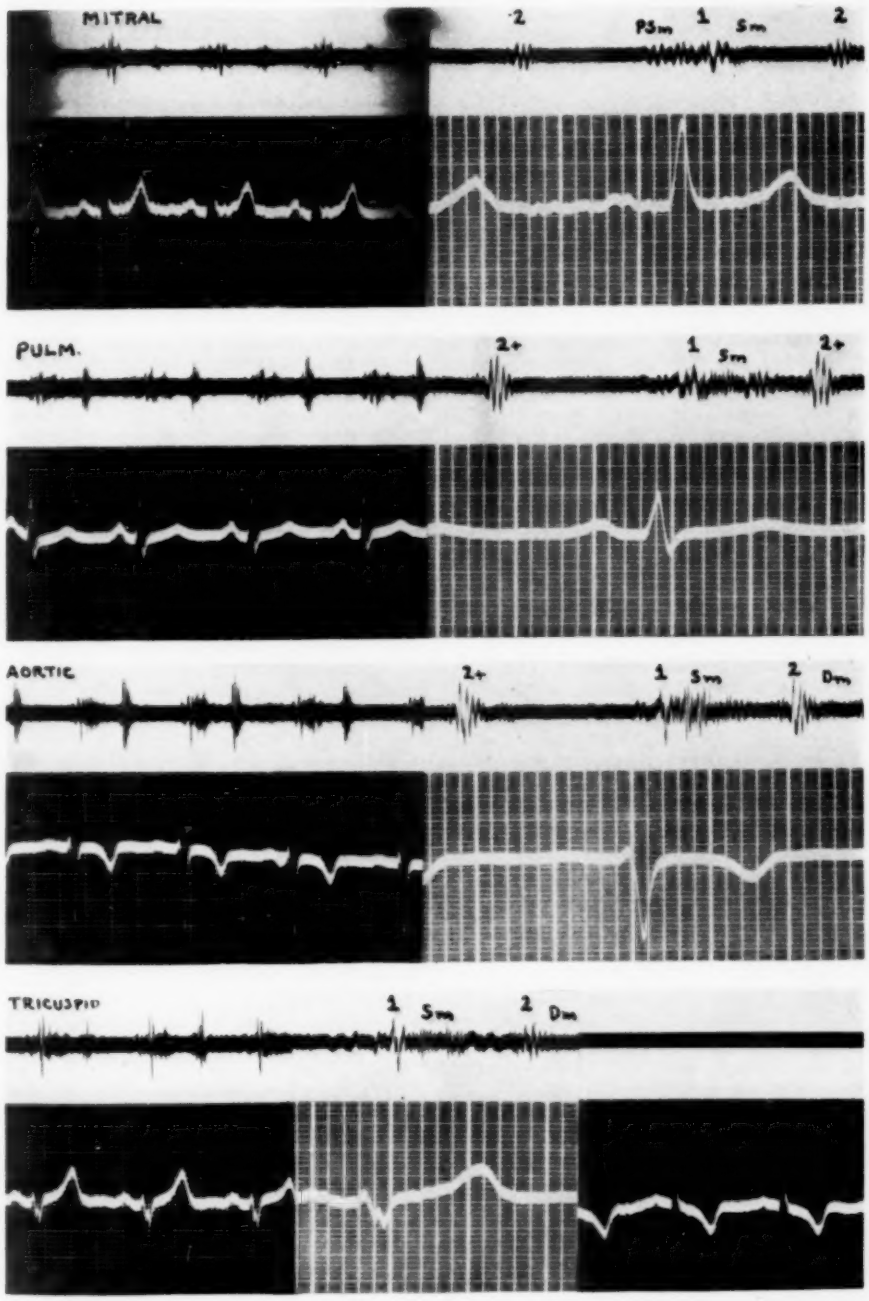


FIG. 3. Case 3.

could not be heard with the acoustic stethoscope but was easily recognized with the aid of an amplifying stethoscope. This murmur was too low pitched to be recognized clinically, being in the neighborhood of 50 vibrations per second. The systolic

murmur, of about 100 vibrations per second, was easily heard. The electrocardiogram revealed reciprocal S–T interval and T-wave changes in Leads I and III with left axis deviation; chest leads suggesting coronary disease with, possibly, an old occlusion.

*Case 4.* White female, aged 53, on December 2, 1939, complained of progressive dyspnea on exertion, palpitation and vertigo during the previous six months. After walking two blocks, choking spells with inability to get her breath, cough and weakness forced her to rest, the dyspnea lasting from one half to two hours. At times a sharp sticking precordial pain, lasting only a few minutes, occurred. She also complained that her fingers would turn blue and feel numb. Orthopnea, congestive failure, bilateral edema of the legs and thighs and distention of the abdomen were evident. The heart was irregular at the rate of 40 to 50 per minute. Blood pressure was 200 mm. Hg systolic and 114–110 mm. diastolic. The left heart border was at the anterior axillary line. Marked pulsation of neck vessels was noted. A loud systolic murmur was heard all over the precordium with a systolic thrill in the aortic area.

Stethogram (figure 4) showed a loud crescendo-decrescendo systolic murmur in all areas, emphasized in the aortic area and without normal heart sounds. The first sound in the mitral area had practically disappeared; the second sound was scarcely audible. The first sound in the pulmonic area was reduplicated and the second sound submerged in the systolic murmur which ran into a faint inaudible diastolic murmur. The aortic first sound was present but indistinct; the second sound was absent. The diastolic murmur noted in the pulmonic area was more distinct in the tricuspid area. The marked deformity and obliteration of heart sounds in complete heart block, which so often make it impossible to differentiate a systolic from a diastolic murmur, are well illustrated. Gross distortion of heart sounds is associated with organic not functional murmurs. A stethogram simplifies interpretation.

*Case 5.* White female, aged 30, on April 19, 1937, complained of progressive shortness of breath of three years' duration. She had had scarlet fever, repeated sore throats, diphtheria and influenza as a child. During the "influenza" she had "aches in her joints" but no other history suggesting rheumatic fever.

She appeared chronically ill, undernourished and weak. Pulse was 100 and regular. Blood pressure was 100 mm. Hg systolic and 74–70 mm. diastolic. Mucosa was pale. Skin was dry. There was slight bilateral ankle edema. The heart was slightly enlarged to right and left. The apex beat in the fifth interspace was just outside the left midclavicular line. A presystolic mitral thrill with long presystolic murmur was noted. The diagnosis was rheumatic heart disease with mitral stenosis. A typical mitral stenosis sound track is seen (figure 5) with large $P_2$, notched $P_2$, significant T-wave changes, and a tendency to right axis deviation in the electrocardiogram. The second sound in the mitral area is scarcely visible. The pulmonic second sound is only slightly accentuated. The record coincides with a sketch, previously made, of the heart sounds. Stethography is an invaluable aid in teaching the student to recognize, differentiate and readily to correlate the various sounds heard over the heart. It serves as a constant check on clinical findings.

*Case 6.* White male, aged 45, when first seen October 24, 1929, complained that heart trouble followed quinsy 20 years before with progressive shortness of breath, swelling of the ankles, cough and nausea during the previous four weeks. Rheumatic fever was not otherwise suggested.

He was acutely ill. The cervical veins were distended and pulsating irregularly. Ears, lips and fingers were cyanotic. The left heart border was 6 cm. beyond the midclavicular line, the right border 4 cm. to the right of the right sternal edge. Apex beat was seen and felt in the sixth interspace at the midaxillary line. An apical pre-

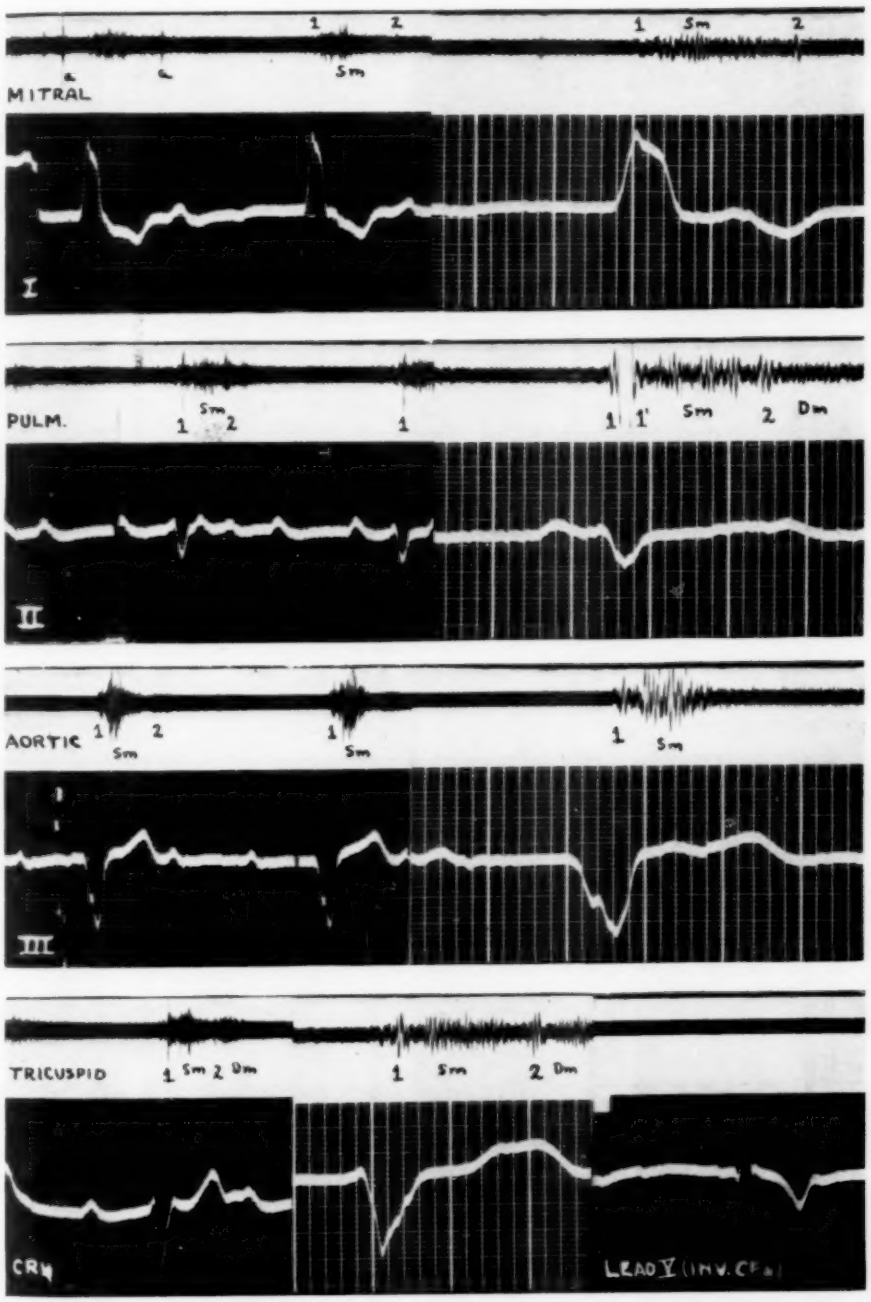


FIG. 4. Case 4.

systolic thrill was felt. The pulmonic second sound was accentuated. The liver edge was 3 cm. below the costal margin. Pulse was irregular at 70 to 80 per minute. Blood pressure was 150 mm. Hg systolic and 105–100 mm. diastolic. Reduplication

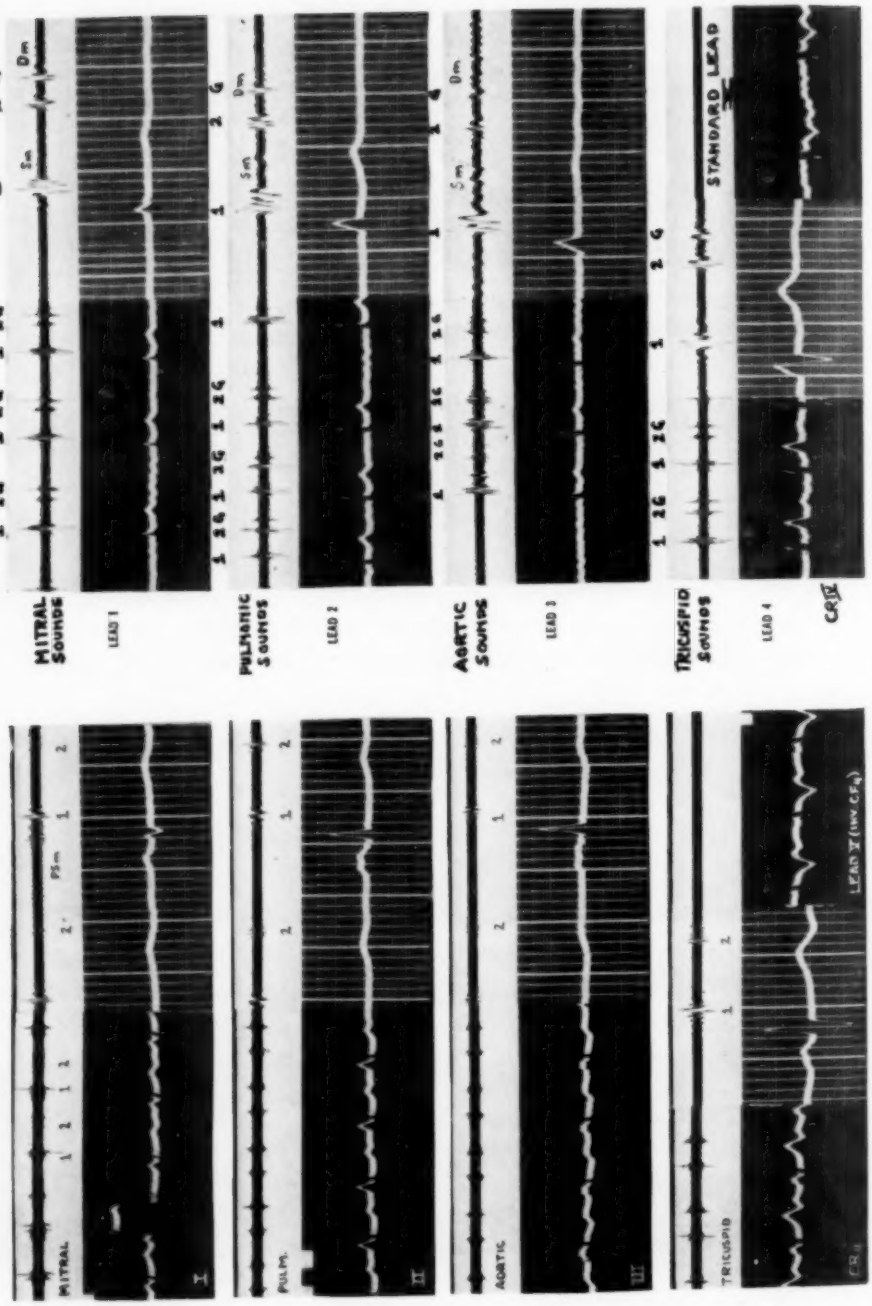


Fig. 6. Case 6.

Fig. 5. Case 5.

of the second sound, heard at the apex, was considered to be either a gallop rhythm or the opening snap of a mitral stenosis.

The electrocardiogram shows auricular fibrillation. The stethogram reveals a protodiastolic gallop rhythm (figure 6). Previous sound curves, without synchronized electrocardiograms, failed to show the true nature of this third sound. A systolic and diastolic murmur is present. A prominent auricular sound is seen in the mitral area.

## Discussion

We have correlated the clinical, electrocardiographic, stethographic and cardioscopic findings and conclude that the method is an invaluable aid in the early diagnosis and detection of heart disease. The method is simple, economical, and gives precise information unobtainable by other means. The diagnostic technic is readily applicable to the routine examination of recruits, to the routine screening of large populations, and to bedside and consultation practice. This practical and useful diagnostic aid undoubtedly will reveal many early cases of heart disease. At present there seems to be little excuse for avoiding the use of graphic methods in the study of heart disease. They increase accuracy in diagnosis. Due to limitations of hearing, it is well that our auditory acuity can be checked and rechecked. Serial changes in stethograms and electrocardiograms occur in acute coronary occlusion, coronary sclerosis, active rheumatic endocarditis, subacute bacterial endocarditis, patent ductus arteriosus, as well as in obesity, hypertension and anemia. In more than half of our cases the electrocardiogram gave valuable information; in more than one-third of the cases the stethogram was helpful. Hence, it is reasonable to conclude that these graphic methods were of definite value in three out of four cases examined. The value of combined graphic methods in the diagnosis of heart disease is emphasized by the fact that the original Wassermann test was but 80 per cent efficient in detecting syphilis. With improvement in equipment, technic may be further simplified, and with more training and experience, interpretation of findings so improved, that more frequent recognition may prevent much of the damage now resulting from unrecognized rheumatic and coronary heart disease.

## Conclusions

1. Combined graphic and cardioscopic diagnosis in conjunction with the routine clinical examination constitutes a practical plan for the early recognition of heart disease.

2. The results of combined electrocardiography, stethography and cardioscopy in the examination of 1108 cases of heart disease are reported and discussed.

3. A simplified chest lead technic is described. Chest lead abnormalities occurred in 29 per cent of the cases. These abnormalities were directly proportional to the age of the patient, being found in 20 per cent of those

Fig. 6. Case 6.

Fig. 5. Case 5.

between 31 and 41 years of age, and in 47 per cent of those between 61 and 87 years of age.

4. Organic heart murmurs are usually associated with heart sound abnormalities and often with changes in the electrocardiogram. Graphic methods are of value in differentiating organic and functional murmurs.

5. A diastolic murmur may be confused with a systolic murmur when the first heart sound is inaudible.

6. A stethogram is essential for the accurate diagnosis of gallop rhythm.

7. A stethogram differentiates a presystolic murmur from a "roughened" first sound.

8. In 88 per cent of 1108 cases clinical findings coincided with graphic findings.

9. In 12 per cent of 1108 cases the stethogram was essential for the diagnosis of gallop rhythm, of early mitral stenosis or of early aortic disease.

10. Of 102 cases of gallop rhythm, 42 per cent were misjudged clinically so far as timing the extra sound was concerned.

11. A double-beamed cardioscope for the instantaneous visualization of stethogram and electrocardiogram is predicted as a diagnostic adjunct in the rapid examination of recruits, applicants for flight training, insurance and in screening for unrecognized heart disease.

12. Six typical cases are reported. Results of clinical examination, correlated with graphic findings, demonstrate the value of the method for the early diagnosis of heart disease.

13. Serial stethograms, like serial electrocardiograms, are useful in following the course of heart disease. A comparison of records from the same patient or from other cases with the same disease is frequently of value.

14. Cardioscopy as well as combined stethography and electrocardiography aids in teaching, since visual impressions are always superior to verbal descriptions.

15. This method of diagnosis is young but it will grow. Stethography has already arrived at a stage comparable to electrocardiography during the third decade of its development.

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# SYNDROME OF RUPTURE OF AORTIC ANEURYSM INTO THE PULMONARY ARTERY; REVIEW OF THE LITERATURE WITH REPORT OF TWO CASES *

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The incidence of rupture of an aortic aneurysm into the pulmonary artery is of rare enough occurrence to warrant publication by most clinicians of their respective cases soon after discovery. Even rarer is the antemortem diagnosis of such a condition, because the diagnostician is either unfamiliar with the syndrome or discards the possibility in favor of a more statistical probability.

The terminology "arteriovenous" aneurysm or anastomosis with reference to the great vessels leaving the heart is not preferable. Although it is true that with regard to the circulating blood in a communication between pulmonary artery and aorta there is a mixing of arterial and venous blood, it is the general consensus of opinion that the term "vein" must adhere to two fundamentals: a carriage of unoxygenated blood and a return of this blood to the heart. Since the communication between the two vessels involved here follows only one of these principals, i.e., the carriage of unoxygenated blood, and is technically an artery since it carries blood away from the heart, we are of the opinion that "arterio-arterial anastomosis" or "arterio-arterial aneurysm" is more applicable to the condition of the shunt of blood from an aneurysm of the aorta into the pulmonary artery.

Since the diagnosis of a rupture of an aortic aneurysm into the pulmonary artery is based upon several essential and definite criteria, all of which are quite obvious and easily discernible to even the most inexperienced, it is only necessary to call attention to the existence of such a syndrome in order to simplify a diagnosis. Such is the purpose of this paper.

## History

That such an "arterio-arterial" aneurysm is indeed uncommon is evidenced by the fact that there exist in the literature only 81 cases, including clinical, autopsy reports, and museum specimens. As White [61] stated in a recent article, the majority of the patients reported are to be found in the past century. A total of 54 have been mentioned in the literature from 1812–1900. During the past 41 years only 27 have been published, and of these only four have been diagnosed antemortem (Scott,[48] 1924; White,[61] 1941; Porter [40] (2 cases), 1941). Two more were correctly diagnosed at

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the Charity Hospital of Louisiana in New Orleans in 1941. Wade [57] recognized one case before death in 1861.

Probably the earliest account of an aortic aneurysm rupturing into the pulmonary artery is one related in the Bulletin de la Faculté de Médicine de Paris in 1811 by Drs. Payne and Zink in which the sac is supposed to have "s'ouvrant" into the pulmonary artery. Peacock,[37] however, states that in this case it only appears to have projected into the vessel and not to have communicated directly with it. For that reason this case was eliminated in this analysis. In 1812, Wells [59] recorded a case seen by Baillie in which such a rupture occurred. Munro [22] in 1839 described a patient with an "arterio-arterial" aneurysm and in 1840, Reid [43, 44, 45] added three more cases to the sparse literature: two with ruptures into the main trunk of the pulmonary artery and one between the descending aorta and the left pulmonary branch. This latter case is of interest in that the author states that the site of communication corresponded exactly with the site of the fetal ductus arteriosus. This brings up the controversial subject of congenital origin versus a communication resulting from a ruptured aneurysm. Thurman [55] in 1840 reviewed the reports of spontaneous varicose-aneurysms of the ascending aorta and discussed five instances of communication between the pulmonary artery and aorta. In 1868 Peacock [37] summarized the literature and was able to find 19 patients with this type of communication. Since that time, reports of this syndrome have emerged in the literature at intervals with occasional surveys. In 1907 Kappis [24] in Germany reviewed 32 cases and added one of his own. Among the first patients reported in this country was one by Hollis [20] in 1908. This was quickly followed by other reports from different medical centers of the United States. The latest were those of White,[61] Porter,[40] and Mallory.[33]

In reviewing the literature it was found that the majority of the reports were in the English journals, with only 11 in the German literature, three in the French, and one in the Portugese (Brazilian), and one in Spanish (Argentine).

## Incidence

*General Incidence from the Literature.* As mentioned above only 81 cases have been reported in the literature. The patients from Charity Hospital bring the total to 83. The close relationship between the two great vessels offers ample opportunity for communication between them, and considering the frequency of aneurysms of the ascending and transverse aorta, one wonders at the low incidence of rupture into the pulmonary artery. The possibility that this occurs more frequently than is reported is probably explained by the failure to recognize this condition clinically, the neglect on the part of the pathologist to open the pulmonary artery unless clinical evidence so indicates, and lastly the possibility of leaking or pinpoint communication which even the most diligent and scrupulous inspection may fail to reveal.

A factor which might likewise tend to account for the low occurrence of such a communication, even in the face of the close anatomical relationship, is the more frequent occurrence of aneurysms of the ascending aorta in the anterior and right aspects of the vessel rather than in the left and posterior parts.[4]

From a review of the literature in the 65 patients reported in which the sex was stated, the occurrence in males was 59 cases, 91 per cent, as contrasted to that of only six females, 9 per cent. This is probably explained upon the basis of greater frequency of aneurysms in males and upon the more prevalent amount of physical strain to which the male is exposed.

Boyd [4] in a perusal of 4000 thoracic aneurysms found only 45 communications between the aorta and the pulmonary artery, an incidence of 3.7 per cent of all points of rupture. Lemann [29] found a closely allied percentage, 3.04 per cent of 592 selected cases from the literature. However, in a review of 2000 case records at the Charity Hospital between the years 1905 and 1914, he found only 52 thoracic aneurysms with 11 ruptures and none into the pulmonary artery. Delp [10] of the University of Kansas, in 6099 autopsies (of which there were 85 thoracic aneurysms), found only one instance.

*Incidence at the Charity Hospital of Louisiana in New Orleans.* From the records of the Charity Hospital (table 1) only two were found between June 30, 1911, and December 31, 1941, which showed definite evidence of rupture of an aortic aneurysm into the pulmonary artery. There was one case in which a communication between the two vessels resulted from an aneurysm of the left pulmonary branch that ruptured into the aorta. This case is not included in this analysis.

During the period between 1911 and 1941 there were 1,052,667 hospital admissions and approximately 23,239 autopsies. The total number of aneurysms of the aorta in this interval was 1393 and of this 219 were of the thoracic aorta. During this period 110 of the 219 thoracic aortic aneurysms ruptured (table 1). Thus the incidence in 30 years of rupture of an aortic aneurysm into the pulmonary artery in this survey is about 0.91 per cent of all thoracic aortic aneurysms, and 1.83 per cent of all ruptured thoracic aortic aneurysms.

## Pathology

*Anatomical Considerations.* The anatomical relations of the aorta and pulmonary artery are such that all three parts of the thoracic aorta are in contact with the pulmonary artery or its branches as far as the middle part of the descending thoracic aorta. At its origin from the conus arteriosus of the right ventricle, the pulmonary artery extends obliquely upward and backward, passing at first in front of and then to the left of the ascending aorta. At the under surface of the arch, the pulmonary artery divides into right and left branches, the right passing posterior to the ascending trunk and the left passing anterior to the descending trunk of the aorta.

TABLE I

Incidence of Rupture of Aortic Aneurysms (Thoracic and Abdominal) Over a Period of 30 Years (1911–1941) from 1,393 Cases of Aortic Aneurysm at The Charity Hospital of Louisiana at New Orleans

| Portion of Aorta Involved | Aneurysm Rupturing into: | Number | Percentage | |
|---|---|---|---|---|
| | | | Of Total Thoracic Aneurysms | Of Total Abdominal and Thoracic Aneurysms |
| *Thoracic* Ascending | | | | |
| | Esophagus | 2 | 1.8 | 1.4 |
| | Right bronchus | 4 | 3.6 | 2.9 |
| | Left bronchus | 3 | 2.7 | 2.1 |
| | Pericardium | 9 | 8.2 | 6.4 |
| | Trachea | 4 | 3.6 | 2.9 |
| | Right pleural cavity | 2 | 1.8 | 1.4 |
| | Left pleural cavity | 4 | 3.6 | 2.9 |
| | Right lung | 1 | 0.9 | 0.7 |
| | Pulmonary artery | 1 | 0.9 | 0.7 |
| | Total | 30 | 27.1 | 21.4 |
| Transverse | | | | |
| | Esophagus | 11 | 10.0 | 7.9 |
| | Left bronchus | 4 | 3.6 | 2.9 |
| | Pericardium | 3 | 2.7 | 2.1 |
| | Trachea | 6 | 5.5 | 4.3 |
| | Right pleural cavity | 3 | 2.7 | 2.1 |
| | Left pleural cavity | 10 | 9.1 | 7.1 |
| | Left lung | 1 | 0.9 | 0.7 |
| | Right lung | 2 | 1.8 | 1.4 |
| | Externally | 2 | 1.8 | 1.4 |
| | Pulmonary artery | 1 | 0.9 | 0.7 |
| | Total | 43 | 39.0 | 30.7 |
| Descending | | | | |
| | Esophagus | 7 | 6.4 | 5.0 |
| | Left bronchus | 3 | 2.7 | 2.1 |
| | Trachea | 1 | 0.9 | 0.7 |
| | Right pleural cavity | 5 | 4.5 | 3.6 |
| | Left pleural cavity | 16 | 14.5 | 11.4 |
| | Aorta (dissecting) | 1 | 0.9 | 0.7 |
| | Right lung | 2 | 1.8 | 1.4 |
| | Mediastinum | 1 | 0.9 | 0.7 |
| | Peritoneum | 1 | 0.9 | 0.7 |
| | Total | 37 | 33.5 | 26.3 |
| | Total Thoracic | 110 | | 78.4 |
| | | | Of Total Abdominal Aneurysms | |
| *Abdominal* | | | | |
| | Peritoneum | 14 | 46.7 | 10.0 |
| | Retroperitoneal space | 12 | 40.0 | 8.6 |
| | Left pleural cavity | 3 | 10.0 | 2.1 |
| | Right pleural cavity | 1 | 3.3 | 0.7 |
| | Total | 30 | | 21.4 |
| Total Ruptured Aortic Aneurysms | | 140 | | |

As mentioned above, this close relationship of the pulmonary artery and the ascending, transverse, and upper part of the descending aorta offers ample opportunity for communication between the two. This anatomical consideration is important in that even with this close approximation of the two great vessels added to the frequency of aortic aneurysms in these areas, rupture into the pulmonary artery occurs in only a very small percentage of cases. Some explanation of this has been mentioned above.

*Site of the Aneurysm.* Boyd [4] has referred to the more frequent occurrence of aneurysms of the ascending aorta upon the anterior and right aspects of the vessel rather than upon the posterior and left. In the latter site the sac would be in close approximation to the pulmonary artery. In the arch of the aorta the greater frequency of occurrence is in the inferior

TABLE II

Incidence of Site of Rupture of Aneurysm of the Thoracic Aorta from Three Selected Studies and One from The Charity Hospital. (Modified from Delp.)

| | Delp[10] | Lemann[29] | Boyd[4] | Charity Hospital |
|---|---|---|---|---|
| No. of Autopsies | 6,099 | 2,000 | * | 23,239 |
| No. of Thoracic Aneurysms | 85 | 52 | 4,000 | 219 |
| No. of Ruptured Aneurysms | 46 | 11 | 1,197 | 110 |
| Rupture Site: | | | | |
| Pericardium | 28 | 2 | 369 | 12 |
| Left thorax | 13 | 1 | 174 | 30 |
| Right thorax | | 1 | 88 | 10 |
| Bronchial tree | 1 | 3 | 171 | 25 |
| Esophagus | 1 | 3 | 112 | 20 |
| Pulmonary artery | 1 | — | 45 | 2 |
| Superior vena cava | — | — | 44 | — |
| Mediastinum | 3 | — | 20 | 1 |
| Externally | 1 | — | 61 | 2 |
| Right lung | — | — | 12 | 5 |
| Left lung | — | 1 | 40 | 1 |
| Miscellaneous | 1 | — | 61 | 2 |

* Only selected thoracic aneurysms.

and posterior regions of the vessels.[4] The explanation of this is not well understood, but one may postulate the formation of an aneurysmal sac along the lines of least resistance.

Boyd [4] states that the frequency of occurrence of aneurysm of the aorta is in the relation of 10 in the ascending, seven in the arch, three in the descending, and one in the lower thoracic aorta. Lemann [29] from his series of cases found the arch to be the most frequent site with the descending next and the ascending last. In the series of cases of ruptured aneurysm at Charity Hospital (table 1) between 1911–1941, the incidence was higher in the arch, 30.7 per cent, with 26.3 per cent in the descending, 21.4 per cent in the abdominal, and 21.4 per cent in the ascending aorta.

However, a review of the reports in the literature of rupture of an aortic aneurysm into the pulmonary artery indicates that the majority communicated through a rupture of an aneurysm of the first part of the thoracic aorta (tables 3 and 4). Of the reported cases (74) in which the site of the

TABLE III

Cases of Rupture of an Aortic Aneurysm into the Pulmonary Artery, From a Review of the Literature.
A total of 81 cases has been mentioned in the literature since 1812, including museum specimens.

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Wells[59] | 53 | M | ? | Sudden onset after walking and playing with children. 3 yrs. cardiac disease | — | — | — | — | — | — | — | — | — | 1st part of descending aorta. Size of orange | 8–9 hrs. | Aorta adhered to pulmonary artery. Ragged opening ½ in. long in aorta communicating with pulmonary artery. |
| 2. Thurman[55] | 33 | M | — | Sudden while lifting a heavy load. Giving away in chest | Face pale, lips vivid | Marked dyspnea | Cough with visco-sanguinous sputum | Lower extremities | Pain in chest extending to spine | Jerking pulse | Continuous sawing in 2nd left interspace | Purring tremor at 2nd left interspace | — | 1st part ascending aorta | 11 wks. | Aneurysm projected into mouth of right ventricle and into pulmonary artery. Two openings between aorta and pulmonary artery. |
| 3. Reid[43] Case 1 | 36 | M | — | No history of onset. Cardiac symptoms for six months | — | — | — | — | — | — | — | — | — | 1st part descending aorta | Died soon after admission | Opened into pulmonary artery (left) by rounded, smooth edged aperture. Not believed to be a reopened ductus arteriosus. |
| 4. Reid[44] Case 2 | 60 | M | — | Sudden onset. General cardiac symptoms previously | — | — | — | — | — | — | — | — | — | Ascending aorta. Size of orange | Few hours | Pressed on left auricle. Opened into pulmonary artery by a long tear 1.3 in. in length. |
| 5. Reid[45] Case 3 | 53 | M | — | Sudden onset. Bronchial symptoms for several months | — | Marked dyspnea. Loss of consciousness | — | — | — | — | — | — | — | Ascending aorta. Size of fist | 4 mins. | Opened into pulmonary artery by a ragged fissure 1¼ in. long. |
| 6. Turnbull[56] | 41 | M | — | Sudden onset following a fall | — | — | — | — | — | — | Continuous murmur | Purring tremor at base | — | Ascending aorta above valves | 5 mo. | One opening into pulmonary artery and one into right ventricle. |
| 7. Munro[22] | 24 | M | — | Sudden onset following pneumonia | Tumid and livid | Marked dyspnea and palpitation | Cough and expectoration | Abdomen and lower extremities extending to anasarca | — | "Large thrilling" | Continuous over whole chest | — | — | Ascending aorta | 10 wks. | Two openings into pulmonary artery. |

* indicates those instances diagnosed before death.
\+ under the column labeled "Syphilis" indicates the presence of syphilis in the patient.
\+? indicates questionable syphilis.

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8. Smith [50] | 22 | M | — | Sudden onset with vertigo and syncope | Face pale, lips cyanotic | Orthopnea and palpitation | — | Edema of face | Precordial pain | Intermittent | Systolic murmur | Intense over whole chest | — | 1st part ascending aorta | 4 mo. | Small opening into pulmonary artery with rounded edges. |
| 9. Rokitansky [47] Case 1 | 41 | M | — | — | — | — | — | — | — | — | — | — | — | Ascending aorta. Size of walnut | Sudden death | Opened by triangular aperture with ragged edges into pulmonary artery. |
| 10. Rokitansky [47] Case 2 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | Opening into pulmonary artery. |
| 11. Rokitansky [47] Case 3 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | Communication between aorta and right pulmonary artery. |
| 12. Rokitansky [47] Case 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | Communication between aorta and right pulmonary artery. |
| 13. Rokitansky [47] Case 5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | Communication between aorta and right pulmonary artery. |
| 14. Ogle [36] | 27 | F | — | Sudden onset in cardiac condition | Face pale, lips cyanotic | Marked dyspnea, palpitation | Cough with hemoptysis | — | — | Jerking | Systolic in 3rd left interspace | Thrill in systole | — | Ascending aorta. Size of hen's egg | 2 mo. | Aperture size of quarter opening into pulmonary artery. |
| 15. Herapath [18] | 53 | M | — | Sudden onset following vomiting | — | — | — | — | — | — | — | — | — | Arch and descending aorta | 1–2 hours | Lacerative aperture 1 in. long connecting aorta with pulmonary artery. |
| 16. Bennett [3] | 33 | M | — | Sudden. "Giving away in chest" | — | Marked dyspnea | Cough and hemoptysis | Anasarca | Chest pain at onset | Irregular | Continuous blowing murmur | — | — | 1st part ascending aorta. Size of walnut | 5 mo. | Transverse communication between aorta and pulmonary artery. |
| 17. Pierreson [39] | 61 | M | — | Sudden onset with pain in chest | Lividity of face and lips | Orthopnea | — | Lower extremities | Onset with pain in chest | Corrigan | Systolic murmur | Tremor in 2nd left interspace | — | Ascending aorta | 1 yr. | Bilocular aneurysm 3 cm. above aortic valves. Small communication between aorta and pulmonary artery. |
| 18. Wade [*] [57] | 35 | M | — | Sudden onset following exertion | — | Dyspnea | Cough. Hemorrhage from rectum | — | — | — | Double murmur in upper left chest | Purring tremor in upper left chest | — | 1st part ascending aorta. Size of hen's egg | 2 mo. | Communication with pulmonary artery via a slit "3 lines long." Smooth, rounded aperture. Second opening into right ventricle. |
| 19. Roberts [46] | 28 | M | — | Sudden onset. Signs of cardiac disease | Lips livid, face pale | Orthopnea | Cough and hemoptysis | Legs, thighs, ascites | — | Quick, jerking | Continuous murmur | Continuous thrill | — | 1st part ascending aorta | 2 mo. | Funnel shaped aneurysm. Communication between vessels size of a pea. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20. Peacock [37] | 26 | M | — | Sudden onset with epigastric pain | Lips livid, cheeks flushed | Increasing dyspnea | Cough | Anasarca | Intense pain in epigastrium | Corrigan | Double murmur | — | — | 1st part ascending aorta. Size of large hen egg | 2 mo. | Smooth orifice "2 lines wide and 4 lines long." Evidence of erosion and not sudden rupture. |
| 21. Taylor [53] | 39 | M | — | Gradual onset during bad weather | Jaundice | Orthopnea | — | Lower extremities and ascites | Pain in chest at onset | Rapid but not collapsing | Double murmur at 2nd left interspace | Systolic | — | Ascending aorta, size of large walnut | 48 hrs. | Communication between vessels by way of a long rent ½ inch in length. |
| 22. Taylor [54] Case 1 | 30 | M | — | Sudden after severe vomiting | "Negroid" appearance | — | — | — | Pain in precordial area | Scarcely perceptible | — | — | — | Arch of aorta | 2 hrs. | Small area of communication between aorta and pulmonary artery. |
| 23. Taylor [54] Case 2 | 45 | M | — | Sudden onset with fluttering in left hypochondrium | Face and lips pale. Slight malar flush | Inspiratory dyspnea (oliguria) | Cough with hemoptysis | Anasarca | Pain in epigastrium | — | Systolic at 2nd left interspace | Systolic thrill in 2nd left interspace | — | Ascending aorta | 8 wks. | Small aperture with smooth rounded edges between aorta and pulmonary artery. |
| 24. Taylor [54] Case 3 | 44 | M | + | Sudden onset with severe symptoms | "Dusky" face, congestion of lips | Dyspnea | Cough | Anasarca | Severe precordial pain 2 yrs. prior to admission | Corrigan | To and fro murmur down sternum | — | — | Ascending aorta. Size of fetal head | 2 yrs. (5 days after admission) | Main sac had 2 secondary pouches, one of which opened into the pulmonary artery through a small aperture. |
| 25. Taylor [54] Case 4 | ? | M | + | Sudden onset with weakness | Livid face | Dyspnea | Slight cough with hemoptysis | Lower extremities | Pain over precordium | Feeble pulse | Double murmur in 2nd–3rd left interspaces | Systolic | — | Ascending aorta | 9 mo. | Adhesion of pulmonary valves to aneurysm. Communication between aorta and pulmonary artery through a smooth edged aperture 5 mm. in diameter. |
| 26. Taylor [54] Case 5 | 40 | M | +? | Sudden onset while lifting hides | Lividity of face and lips | Dyspnea | Cough with hemoptysis | Anasarca | Pain in precordium | Corrigan | Systolic in left 3rd–4th interspaces | Systolic in left 2nd–3rd interspaces | — | Ascending aorta | 12 mo. | Aneurysm separated from pulmonary artery by thin septum which is beginning to rupture—a leaking aperture. |
| 27. Taylor [54] Case 6 | 45 | M | — | Sudden onset 3 wks. after hard labor | Lividity | Dyspnea | Cough with mucopurulent sputum | Lower extremities | Pain in left chest | Corrigan | Roaring musical bruit at base. Continuous | No thrill | — | Ascending aorta | 4 mo. | Small opening 2½ mm. in diameter opening into pulmonary artery. |
| 28. Taylor [54] Case 7 | 43 | M | + | Gradual with cardiac signs | Pallor | Great dyspnea (oliguria) | — | Anasarca | Tightness in chest | Regular and compressible | Systolic | — | — | Ascending aorta | ? 6 yrs. (4 days after admission) | Opened into pulmonary artery by one old aperture and one recent rupture; third opening doubtful. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 29. Murchison [35] | 48 | M | — | Sudden onset after severe fall | Extreme lividity of face. Body pale | Dyspnea (palpitation, euphoria) | Cough | Anasarca | No pain | Feeble but regular | Systolic "bellows-like" over whole chest | — | — | Ascending aorta | 7 mo. | Communicated with pulmonary by circular aperture 1½ in. above valves. |
| 30. Cayley [6] | 37 | M | — | Sudden onset; no precipitating factor | Great lividity | Dyspnea | — | Legs and ascites | Severe pain in left chest | Corrigan | Double "bellows" murmur 2nd left interspace | — | — | Ascending aorta. Size of walnut | 1 mo. | Communicated with pulmonary artery through a smooth rounded orifice 1¼ in. in diameter. |
| 31. West [69] | 38 | M | — | Sudden onset | — | Dyspnea | Cough | — | Severe in left chest | — | Double in 3rd–4th left interspaces | Coarse thrill left 3rd–4th interspaces | — | Ascending aorta. Size of egg | 10 wks. | Communication between aorta and pulmonary artery via aperture ½ in. in diameter. |
| 32. Hanford [16] | 35 | M | — | Sudden onset | — | Orthopnea | Cough, abundant frothy sputum | Lower extremities | Precordial pain | Irregular, small, feeble, fluttering | Harsh systolic at 3rd left interspace | Systolic in 3rd left interspace | — | Ascending aorta | — | Communication between aorta and pulmonary artery through aperture size "three-penny piece." |
| 33. Lamplough [39] | 27 | F | + | Sudden onset while climbing stairs | Face pale, lips livid | Orthopnea | Cough and hemoptysis | Anasarca | Pain across chest and between shoulders | Corrigan | Continuous murmur in 2nd left interspace | Prolonged systolic in 2nd, 3rd, 4th left interspaces | — | Ascending aorta. Size of pullet's egg | 4 mo. | Communication between aorta and pulmonary artery via 2 small rounded orifices. |
| 34. Gairdner [15] Case 1 | 42 | M | +? | The patient was a blacksmith. No clinical history is given. The aneurysm was on the ascending aorta, about the size of a chestnut, and projected directly against and pushed into the first part of the pulmonary artery rendering the vessel convex. There was an oval aperture connecting the two vessels, the margins of which were well rounded. | | | | | | | | | | | | |
| 35. Gairdner [15] Case 2 | 31 | M | — | — | Lividity | Dyspnea (oliguria) | — | Anasarca | Great pain in precordium | Irregular. Of low tension | Double murmur | —<br>— | — | Ascending aorta. Size of fist | 1 yr.? | Communication between aorta and pulmonary artery through an oval aperture 1 cm. long. Orifice had well rounded edges. |
| 36. Gairdner [14] Case 3 | 35 | M | — | Sudden onset | Slight pallor | Orthopnea (euphoria, oliguria) | Cough | Anasarca | None | Corrigan | Continuous murmur to left of sternum | Thrill to left of sternum | — | Ascending aorta | — | Small communication between aorta and pulmonary artery. Right heart enlarged. |
| 37. Clarke [7] | 36 | M | +? | Sudden onset | "Slight dusky color" | Orthopnea (euphoria, oliguria) | Cough | Anasarca | None | Not of Corrigan type | Continuous in 2nd and 3rd left interspaces | Continuous 2nd–3rd left interspaces | — | Ascending aorta | — | Small communication between aorta and pulmonary artery. Right heart enlarged. |
| 38. Smith [49] | 31 | M | +? | Sudden onset while on bedpan | Face and lips blanched | Orthopnea | Cough | Upper part chest; neck and head | Pain in chest radiating to neck and head | Absence of radial pulse | None | None | — | Ascending and transverse aorta. Size of orange | 2 hrs. | Communication between aorta and pulmonary artery through a freshly torn aperture. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 39. McNabb[34] | ? | M | +? | Sudden following exertion | — | Dyspnea | Cough and vomiting | Anasarca | — | Rapid, forceful | Loud, rasping systolic murmur at 5th left interspace | — | — | Ascending aorta | 77 days | Communicated with pulmonary artery through an aperture ¾ cm. in diameter. |
| 40. Wooley[62] | 40 | M | + | Sudden onset | (Negro) | Dyspnea to orthopnea | Cough | Lower extremities and trunk | Pain in left chest | Corrigan | Harsh double murmur | — | — | Ascending aorta | 4 mo. | Adherent to pulmonary artery. Communication between vessels through apertures. Edges smooth and rounded. |
| 41. Korb[26] | 53 | M | ? | Sudden onset while climbing stairs | Moderate cyanosis | Dyspnea | — | No edema | Epigastric pain | Barely palpable | Loud systolic murmur at pulmonic valve area | None | — | Ascending aorta | 3 hrs. | Communication between aorta and left branch of pulmonary artery. Ragged aperture 8 cm. from pulmonary valve. |
| 42. Stevenson[52] Case 1 | — | M | + | Sudden onset | (Negro) | Dyspnea | Cough, hemoptysis | Ascites, extremities | Precordial pain | Corrigan | Continuous at pulmonic valve area | Continuous thrill | — | Arch of aorta | 15 mos. | Two communications between aneurysmal sac and pulmonary artery. Each had smooth, rounded edges. |
| 43. Stevenson[52] Case 2 | 26 | M | + | Sudden after wiring of aneurysm | Lips and ears cyanotic. Mucous membranes pale | Dyspnea | Cough | Face and extremities | Pain in chest | Corrigan | Continuous machinery murmur in 3rd left interspace | Systolic thrill | — | Ascending aorta | 4 wks. | Communication between vessels via aperture 6 mm. in diameter. Irregular edges. |
| 44. Stevenson[52] Case 3 | 45 | M | — | Sudden onset. Cold and cough present | (Negro) Pale mucous membranes | Dyspnea to orthopnea | Cough and expectoration | Legs, ankles; ascites | — | Regular but of low tension | Double murmur in 3rd left interspace | Thrill in carotid area | — | Ascending aorta | 3 mo. | Communicated with pulmonary artery through a pin point aperture. |
| 45. Scott[48] Case 1 | 51 | F | + | Sudden onset | (Negro) | Dyspnea | — | Chest, ascites, lower part of body | — | Corrigan | Continuous in 2nd left interspace | Continuous in 2nd and 3rd left interspaces | Aorta normal. Heart enlarged in all directions. Wide at base of heart | Ascending aorta | 2 mo. | Communication between aorta and pulmonary artery by a ragged edged aperture 8 by 6 mm. |
| 46. Scott *[48] Case 2 | 29 | M | + | Sudden onset while at work | (Negro) | Dyspnea | — | Lower extremities | — | Corrigan | Continuous in 2nd left interspace | Systolic thrill at 2nd left interspace | Heart slightly enlarged. No widening at base. Aorta not enlarged. | Ascending aorta | 3 wks. | Communication between aorta and pulmonary artery through ragged edged aperture 1½ cm. in width. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 47. Lenoble [30] | 40 | M | — | Sudden onset | (Negro) Sclerae jaundiced | Dyspnea | Cough | Anasarca | — | Irregular, compressible, small | Double murmur at 2nd left interspace | Systolic at 2nd left interspace | — | Ascending aorta | 11 mo. | Smooth, rounded orifice size of lead pencil connecting aorta and pulmonary artery. |
| 48. Clerc [8] | 40 | M | + | Sudden onset following pneumonia | Intense cyanosis | Dyspnea | Cough | Anasarca | — | Irregular | Systolic in 2nd left interspace | None | Enlarged aortic knob. Enlarged pulmonary conus | Ascending aorta | 4 yrs. | Communication between aorta and pulmonary artery through an aperture 7 mm. in diameter. Edges smooth and rounded. |
| 49. Potter [41] | 53 | M | + | Sudden onset following strenuous exertion | Lips moderately cyanotic | Dyspnea | Cough | Lower extremities | Precordial pain | — | Systolic murmur in 2nd and 3rd left interspaces | Systolic in 2nd and 3rd left interspaces | — | Ascending and transverse aorta | 51 hrs. | Communication between aorta and pulmonary artery via an aperture 1.2 cm. long. |
| 50. Delp [10] | 40 | M | + | Sudden onset while digging in cellar | (Negro) | Paroxysmal dyspnea | No cough | No edema | Substernal pain radiating to back | Corrigan | Harsh, continuous, machine-like murmur in 2nd left interspace | Systolic in 2nd left interspace | Prominent pulmonary conus. Heart enlarged. Aorta not enlarged. *E.K.G.:* Right axis deviation. Diphasic $T_2$, $T_3$. Sinus tachycardia 130/min. Sound tracings showed presence of continuous murmur at left base | Ascending aorta | 48 hrs. | Communication between aorta and pulmonary artery (left branch of pulmonary artery) through a torn, lacerated aperture 2 cm. long. |
| 51. Reeves [42] Case 1 | 36 | M | — | Sudden onset | — | Dyspnea | Cough | Lower extremities | — | Slow pulse | Continuous murmur | — | — | Ascending aorta. Size of orange | 6 mo. | Communication between aorta and pulmonary artery by a long slit. |
| 52. Reeves [42] Case 2 | — | — | — | Sudden onset and sudden death | No clinical symptoms observed | — | — | — | — | — | — | — | — | — | — | — |
| 53. Reeves [42] Case 3 | — | — | — | Sudden onset and sudden death | No clinical symptoms observed | — | — | — | — | — | — | — | — | — | — | — |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 54. Finney [13] | 54 | M | − | Sudden onset | Cyanosis of face, lips pale | Orthopnea | Cough | Lower extremities | No pain | Almost pulseless | Double murmur over entire sternum | — | — | Ascending aorta | 24 hrs. | Communication between aorta and right branch of pulmonary artery. |
| 55. Kraussholdt [27] | 53 | M | − | Sudden onset | Cyanosis | Orthopnea | — | — | Tightness in chest. Headache | Small, regular | Continuous humming murmur | Systolic | — | Ascending and arch of aorta | 1 yr. | Communication between aorta and right branch of pulmonary artery through an aperture 1 cm. long. Dilatation and hypertrophy of heart. |
| 56. Anderson [1] | 33 | M | − | Sudden onset | Pallor and cyanosis. Jaundice later | Dyspnea (oliguria) | Cough, hemoptysis | Lower extremities | Pain in left chest | Corrigan | Blowing double murmur | Thrill in 3rd left interspace | — | Ascending aorta. Size of walnut | 4 wks. | Communication between two vessels through two apertures. Dilatation of heart. |
| 57. Holdmoser [19] | 48 | M | + | Sudden onset with cough | Slight cyanosis | Dyspnea | Cough, hemoptysis | Ascites, lower extremities | Pain and pressure in chest | Fast pulse | Continuous humming murmur | Systolic with diastolic shock. 2nd left interspace | — | Ascending aorta. Size of fist | 6 mo. | Communication between two vessels by wide opening with rounded edges, 1 cm. in diameter. Dilatation of entire heart. |
| 58. Kappis [24] | 44 | M | − | Sudden while at work | Cyanosis | Dyspnea (oliguria) | Cough | Anasarca | Pain in precordium | Corrigan | Double murmur | Systolic thrill | — | Ascending aorta | 6 mo. | Communication between aorta and pulmonary artery through aperture 6 cm. long. |
| 59. Mallory [23] | 47 | M | + | Vague onset of pain in chest | Cyanosis | Dyspnea | No cough | No edema | Recurrent pain in chest | Corrigan | To and fro murmur in 3rd left interspace | Systolic thrill | Dilatation and pulsation of aortic and pulmonary conus. *E.K.G.:* Low ST takeoff in Leads II and IV. Elevated ST in III. Inverted T in Leads I, II, III. No axis deviation | Ascending aorta | 10 days | Aneurysm ruptured into pericardium and pulmonary artery 3.5 cm. above pulmonary valves. |
| 60. Sternberg [31] | 36 | M | + | Gradual onset | Cyanosis of face | Dyspnea | — | Anasarca | Pain in chest | Corrigan | — | No thrill | — | Ascending aorta | 15 wks. | Communication between two vessels through 2 orifices with well rounded and smooth edges. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 61. Correia [9] | 22 | M | + | Sudden onset | Cyanosis | Orthopnea | No cough | Sacrolumbar. Liver enlarged | Intense precordial pain | Corrigan | Harsh continuous murmur in 2nd left interspace | Continuous thrill in 2nd left interspace | Enlarged aorta and pulmonary conus. Total dilatation of heart. *E.K.G.:* No evidence of myocardial disease | Ascending aorta | 2 mo. and 10 days | Communication between aorta and pulmonary artery aperture with well rounded edges 1 cm. in diameter. |
| 62. White [9 61] | 74 | M | + | Sudden onset in a patient with heart disease | (Negro) | Orthopnea | — | Anasarca | Substernal pain | High pulse pressure | Continuous machine-like murmur in 2nd left interspace | Continuous thrill in 2nd left interspace | Enlargement of heart, aorta, and pulmonary conus. *E.K.G.:* "Not remarkable" | Ascending aorta | 8 mo. after clinical diagnosis | Communication between aorta and pulmonary artery through orifice with smooth, well rounded edges 5 by 6 mm. in diameter. |
| 63. Henry [17] | — | M | — | No mention of onset | — | Dyspnea | Cough, hemoptysis, previously | Anasarca | Pain in chest | No inequality of radials | Loud, rasping, prolonged systolic murmur in 2nd left interspace | Marked thrill in 2nd left interspace | — | Ascending aorta | — | Communication between aorta and pulmonary artery by way of oval aperture, long diameter ¼ inch. "Communication probably of long standing." |
| 64. Hollis [20] | 27 | M | — | Sudden onset | Pallor | Dyspnea | Cough | Anasarca | Precordial pain with radiation to interscapular region | Corrigan | Continuous murmur in 2nd left interspace | Double thrill at 2nd left interspace | — | Ascending aorta | 5 mo. | Two apertures communicating between aorta and pulmonary artery. One oval, 5 by 10 cm. with rounded edges; one aperture evidently of recent origin. |
| 65. Jankovich [23] Case 1 | 49 | F | + | Nothing was known of the history of the patient except that she had been in the hospital 11 months previously and was discharged. Between this and the last admission, she became progressively worse and finally entered in a moribund state. A diagnosis of aortic insufficiency was made. The statement was made that the patient probably lived a "long time following rupture." | | | | | | | | — | — | Ascending aorta | — | Heart enlarged. Two openings from aorta into pulmonary artery, the size of a hempseed. These orifices were smooth edged. |
| 66. Jankovich [23] Case 2 | 50 | F | +? | Became "sick" 3 months prior to admission | — | Dyspnea (oliguria) | — | Lower extremities | — | Corrigan | Double murmur at pulmonic valve area | — | — | Ascending aorta. Size of hen's egg | 3 mo. | Hypertrophy of heart. Communication between aorta and pulmonary artery size of a "kronen." Edges of orifice smooth and rounded. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 67. Porter [40] Case 1 | 55 | M | + | Sudden onset following influenza | Moderate cyanosis of lips, mucous membranes, and finger tips | Orthopnea | Cough | Moderate edema of ankles | Pain in right chest | Corrigan | Harsh continuous murmur at 3rd left interspace | Purring systolic and diastolic thrill | Saccular aneurysm of ascending aorta. Heart moderately enlarged and mitral shaped | Ascending and transverse aorta. Size of orange | 12 days | Communication between aorta and pulmonary artery through a rough ovoid opening in aneurysmal sac 1 by 1.2 cm. in diameter. |
| 68. Porter * [40] Case 2 | 50 | M | + | Sudden onset following exertion | No cyanosis | Orthopnea | Dry cough | Sacral, lower extremity edema. Ascites | Sense of constriction in chest | Corrigan | Whirring systolic and less distinct diastolic murmur, in 2nd and 3rd left interspaces | Purring, continuous thrill in 2nd and 3rd left interspaces | Heart enlarged. Aorta enlarged. *E.K.G.:* Sinus tachycardia, 115/min. Right axis deviation | Ascending aorta | 6 mo. | Rounded, almost punched out, orifice 0.7 cm. in diameter connecting aorta with pulmonary artery. |
| 69. Porter * [40] Case 3 | 58 | M | + | Sudden onset | (Negro) | Dyspnea | Dry, brassy cough | Sacral and ankle edema, ascites | No pain in chest | Corrigan | Harsh, whirring continuous murmur at 3rd left interspace | Purring continuous thrill at 3rd left interspace | Heart enlarged. Multiple aneurysms of 3 parts of aorta. Base enlarged. *E.K.G.:* Sinus tachycardia, 107/min. Left axis deviation | Ascending aorta and arch | 2 mo. | Slit-like perforation 1 cm. in length, 2 cm. in width between aorta and pulmonary artery, situated 4.5 cm. above pulmonary valve. |
| 70. Zabludovich [63] | 46 | M | + | Sudden while running | "Cyanatoid" and "erythroid" | Dyspnea | — | Anasarca | Pain in hypochondrium | Small, irregular | Intense double murmur at pulmonary area | Thrill over pulmonary valve area | Right auricle and ventricle enlarged. Aorta and pulmonary conus enlarged. *E.K.G.:* Auricular fibrillation. Biphasic and negative T-waves in all leads. Difference in height of ST in Leads II and III | Ascending aorta | 3 yrs. (?) | Communication between aorta and pulmonary artery through an orifice with ragged edges 4 cm. long. |

TABLE III—*Continued*

| Case | Age | Sex | Syphilis | Onset | Appearance | Dyspnea | Cough | Edema | Pain in Chest | Pulse | Murmur | Thrill | Roentgen-Ray and E.K.G. | Site of Aneurysm | Duration | Autopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 71. Walshe [58] | — | — | — | University College Hospital, museum specimen No. 2254. "According to catalogue, 'was not detected during life by any morbid sound or symptom.' Round smooth opening ½ inch in diameter on aorta and size of split pea on the pulmonary side." | | | | | | | | | | | | |
| 72 to 81. *Museum Specimens* | — | — | — | 2 specimens, Pathological Museum of Western Infirmary, Glasgow: Nos. 57, 58.<br>5 specimens, St. Bartholomew Museum, London: Nos. 1473, 1475, 1476, 1476A and 1477.<br>2 specimens, Museum of Royal College of Surgeons, London: Nos. 3164, 3165.<br>1 specimen, Museum of Faculty of Medicine of Paris. | | | | | | | | | | All cases were of ascending aorta | | |
| 82. Case 1 (Reported in this paper) * | 39 | F | + | Sudden onset with exertion | (Negro) | Orthopnea | Cough and hemoptysis | Anasarca | Precordial pain radiating to left flank | Corrigan | Continuous machine-like murmur at pulmonic area | Systolic and diastolic thrill at pulmonic area | Both ventricles enlarged. Prominent aortic knob and pulmonary conus. Diodrast revealed enlargement of pulmonary artery. *E.K.G.:* Low T-waves in all leads. Diphasic T in Lead IVF. Sinus tachycardia 120/min. Depressed ST in Leads II and III | Arch of aorta. Size of hen's egg | 5 mo. | Aneurysm of arch of aorta at junction of transverse and descending aorta. Communication with pulmonary artery through a small elliptical, smooth edged orifice. |
| 83. Case 2 (Reported in this paper) * | 40 | M | + | Sudden onset while on a motor vehicle | Cyanosis of lips and mucous membranes | Orthopnea | Cough and hemoptysis | No edema | Sense of snapping in chest with pain radiating to left shoulder | Corrigan | Continuous humming machine-like murmur at pulmonary area | Continuous thrill at pulmonic area | Enlargement of heart, aortic knob, and pulmonary conus. Large aneurysm of aorta. *E.K.G.:* Sinus tachycardia 122/min. No definite evidence of cardiac disease | Ascending aorta 6 cm. by 3 cm. | 6 days | Aneurysm of ascending aorta. Filled with laminated clot. Communication with pulmonary through aperture 1 cm. by 2 mm. with ragged, uneven edges. |

aortic aneurysm was mentioned, 63 were of the ascending aorta alone (85 per cent), two were of the arch (3 per cent), six of the ascending aorta and arch (8 per cent), two of the descending aorta (3 per cent), and one of the transverse and descending aorta (1 per cent).

Usually the site may be determined by roentgenography, but frequently no evidence of such a dilatation is observed, and the aneurysmal sac is only found at necropsy.

*Autopsy Findings.* In a large majority of the cases the aorta and pulmonary artery were adherent to each other through adhesions and could be separated only with difficulty. The pulmonary artery was frequently found to be markedly dilated at its point of exit from the right ventricle, in keeping with the hypertrophy and dilation of this chamber. This was true in the cases observed at the Charity Hospital. These observations are in ac-

TABLE IV

An Analysis of 68 Cases of Rupture of an Aortic Aneurysm into the Pulmonary Artery Studied Clinically from the Literature, Including the Two Cases from Charity Hospital. (The number in the parentheses following each symptom or sign indicates the number of patients in which that factor was definitely discussed.)

| Symptoms or Signs | No. of Cases | Per Cent of Cases |
|---|---|---|
| Sex (65) | | |
| Male | 59 | 90.8 |
| Female | 6 | 9.2 |
| Onset (64) | | |
| Sudden (with exertion) | 22 | 34.4 |
| Sudden (with no factor or factors unknown) | 29 | 45.3 |
| Sudden (miscellaneous) | 9 | 14.1 |
| Gradual | 4 | 6.2 |
| Appearance (41) | | |
| Lividity or cyanosis | 27 | 65.9 |
| Pallor | 6 | 14.6 |
| Face pale, lips livid | 5 | 12.2 |
| Jaundice | 2 | 4.9 |
| No change (so stated) | 1 | 2.4 |
| Cough (42) | | |
| Cough (alone) | 20 | 47.6 |
| Cough with expectoration | 5 | 11.9 |
| Cough with hemoptysis | 14 | 33.3 |
| No cough (so stated) | 3 | 7.2 |
| Edema (52) | | |
| Anasarca | 22 | 42.4 |
| Lower extremities only | 12 | 23.1 |
| Lower extremities and ascites | 9 | 17.3 |
| Face only | 1 | 1.9 |
| Chest, neck, head | 1 | 1.9 |
| Face and extremities only | 1 | 1.9 |
| Sacro-lumbar | 1 | 1.9 |
| Lower extremities and trunk | 1 | 1.9 |
| No edema (so stated) | 4 | 7.7 |
| Dyspnea (57) | | |
| Dyspnea (without orthopnea) | 38 | 66.7 |
| Orthopnea | 19 | 33.3 |
| Pain at Onset (45) | | |
| Left chest or precordium (localized) | 25 | 55.6 |
| Chest with radiation to back, head, arms, etc. | 7 | 15.6 |
| Epigastric pain | 3 | 6.7 |
| Tightness in chest | 3 | 6.7 |
| Right chest | 1 | 2.2 |
| Hypochondriac pain | 1 | 2.2 |
| No pain (so stated) | 5 | 11.1 |

TABLE IV—*Continued*

| Symptoms or Signs | No. of Cases | Per Cent of Cases |
|---|---|---|
| Pulse (54) | | |
| Corrigan (collapsing, jerking, large) | 32 | 59.3 |
| Abnormal (other than collapsing, as irregular, rapid, feeble) | 16 | 29.6 |
| Absence of | 1 | 1.9 |
| Not collapsing (so stated) | 2 | 3.7 |
| Regular | 3 | 5.6 |
| Murmur (56) (mainly in 2nd-3rd left interspaces) | | |
| Continuous, humming | 24 | 42.9 |
| Double (systolic and diastolic) | 18 | 33.1 |
| Single (systolic) | 13 | 23.2 |
| None (so stated) | 1 | 1.8 |
| Thrill (44) | | |
| Systolic | 16 | 36.4 |
| Continuous | 9 | 20.5 |
| Systolic and diastolic | 3 | 6.8 |
| Phase not described | 11 | 25.0 |
| None (so stated) | 5 | 11.4 |
| Roentgenography (13) | | |
| Aortic knob enlarged | 10 | 76.9 |
| Aortic knob not enlarged | 3 | 23.1 |
| Pulmonary conus enlarged (Pulmonary conus not mentioned in 5) | 8 | 100.0 |
| Heart enlarged | 10 | 76.9 |
| Heart not enlarged | 3 | 23.1 |
| Site of Aneurysm (including autopsy and museum specimens) | | |
| Ascending aorta | 63 | 85.1 |
| Arch of aorta | 2 | 2.7 |
| Ascending aorta and arch | 6 | 8.1 |
| Descending aorta | 2 | 2.7 |
| Arch and descending aorta | 1 | 1.4 |

cord with those of Holman [21] who in considering the necropsy findings in his cases of patent ductus arteriosus found the pulmonary artery in some instances to be of even greater dimensions than those of the aorta. He also found that the right ventricle invariably was hypertrophied and dilated, concomitant with a dilated right auricle. The latter was not a rule in every case reported in the literature although one patient at Charity Hospital did present a dilated right auricle. This dilation of the pulmonary artery together with the increased size of the right heart may be explained upon the basis of the increased amount of blood in the pulmonary circuit as a result of the abnormal shunt through the arterio-arterial aneurysm. This plus the direction of flow from the aorta to the pulmonary artery as mentioned by Porter [40] determines also the proportional dilation of the artery and right ventricle and possibly the rapidity of right ventricular decompensation (*vide infra*).

Where death results suddenly following rupture, the vessel walls characteristically show a lacerated communication of variable size with ragged torn edges. Conversely, when the rupture follows a slow erosive process, the aperture presents smooth, rounded epithelialized edges, as though of a preformed orifice. The opening is usually oval.

The communication varied in type and size depending upon the nature of the rupture, whether lacerative or erosive. The average size of the orifice

ranged between 0.5 cm. and 1.0 cm. in diameter following erosion and 1.2 and 3.7 cm. in length in those which tore through. With the former, the edges of the aperture were smooth, even, rounded, whereas in the latter, the borders were rough, ragged and uneven. In several cases two or more openings were discovered.

Other tissues and organs at necropsy presented a picture of engorgement typical of that found in right and left ventricular congestive heart failure. The liver was usually enlarged and markedly engorged with blood. The lungs presented a similar picture, and there was a large amount of fluid found in the peritoneal and pleural cavities.

## Disturbed Physiology

Reimann,[25] in discussing the physiologic state existing following the rupture of an aortic aneurysm into the pulmonary artery, presented an excellent description of these factors in the following words: "The effect of short circuiting the blood from an artery to a vein through an aneurysm is quite pronounced and manifested directly or indirectly upon all parts of the body. In general this depends upon the size of the communication and the amount of blood passing through. The changes occurring immediately after a fistula is opened are a fall in arterial blood pressure, increased heart rate, and increased venous pressure. The first is gradually compensated by an increase in the total blood volume, the heart rate decreases, but the action remains more vigorous and the organ hypertrophies. The systolic pressure rises to its previous height or higher, and the diastolic pressure remains low, the pulse pressure is thus increased, and the venous pressure is high. When the heart fails the signs of chronic passive congestion are manifested in all organs."

In the following discussion, an attempt is made to explain some of the outstanding signs and symptoms upon the basis of the disturbed physiology. A percentage occurrence is stated in each instance, the incidence being drawn from the review of the 68 cases sufficiently well described in the literature (tables 3 and 4).

*Murmur.* The majority of cases (56) in the literature presented a murmur of some nature at the second or third left interspaces. In 24 instances (43 per cent), the murmur was a continuous blowing or humming sound crescendo-decrescendo in character, frequently described as "machine-like" and resembling descriptions of the sound heard over a patent ductus arteriosus (*vide infra*). In 18 instances (32 per cent) the murmur was described as double (both systolic and diastolic) with differentiation between the two phases. White [61] states that in his case at first the sound was diagnosed as a double murmur, but that later it was realized that the murmur was continuous in character. This was true in one of the cases (case 1) from Charity Hospital. At first only a murmur in the systolic phase of the cycle was heard. Later a diastolic murmur was also heard. After prolonged

auscultation, it was finally determined that the murmur was continuous throughout the cardiac cycle and no differentiation between the phases could be made. Considering these two instances it is highly probable that many of the reports in the literature were actually of a similar circumstance.

In 13 instances (23 per cent) the murmur was described as systolic only. In one case, there was no murmur heard in the pulmonic area. In the remaining 12 of the 68 cases, either this factor was not mentioned, or the patient died before an examination could be made.

In explaining the continuous murmur heard in this condition Thurman,[55] as early as 1840, stated that as a consequence of the superior force exerted by the left ventricle, the stream of arterial blood is propelled through the aneurysmal orifice with a stronger propagation than that which the blood undergoes during the weaker and more feeble diastole. In addition the elastic reaction of the arterial system is in play during the diastolic period of the heart and thus the murmur is continued during the phase.

Another factor substantiating the expectant probability of a continuous murmur is the greater pressure in the aorta than that in the pulmonary artery. This continuous drive without the possibility of back current [5, 13, 32] produces a *veine fluide* within the pulmonary artery. The eddies are related to the sudden fall in the pressure as the blood passes from one vessel to the other. "These whirling eddies," he states, "are composed of alternating currents of blood under high and low pressure, which set the walls of the vessels as well as the edges of the opening into vibration producing thereby the characteristic thrill and bruit." The above explanation would tend to account for the sudden crescendo and slow decrescendo nature of the murmur. With the increased vigor of contraction (during systole of the heart) the murmur is heard at its loudest; with the relaxation of the ventricle the force is diminished; but although the pressure within the aorta per se drops during the diastole, it remains greater than that in the pulmonary artery, and therefore blood continues to be shunted into the latter with a diminishing velocity, thus setting up fewer and weaker eddies and consequently producing a proportional decrease in the intensity of the murmur. The sound, therefore, continues through diastole in a constant "down-hill manner." Burwell, Eppinger, and Gross [5] stated with regard to the continuous murmur that "Dynamic effects of such magnitude may be expected to produce physical signs. When a large volume of blood passes from a high pressure area to a low pressure area without going through the capillaries, as occurs in the placenta and large arterio-venous aneurysms, murmurs and thrills are produced. In these conditions, as in patients with patent ductus arteriosus, the characteristic murmur is a continuous one with systolic accentuation." The fact that a continuous murmur is not always present is attributed by Lamplough [28] to three factors: (1) disease of the aortic wall, interfering with the elasticity of the vessel, (2) presence of a large amount of blood clot in the aneurysmal sac, and (3) excessive regurgitation through the cardiac aortic orifice in diseased valves, lowering the pressure in the artery beyond.

Taylor [34] states that the murmur depends on the blood pressure about the aneurysmal orifice. An increase in the size of the pulmonary artery may lessen the pressure in this vessel, whereas narrowing of the aorta may increase it here. Taylor assumes that the pressure within an aneurysm is proportionally lower than within its vessels. This lowering of pressures might account for the double murmur heard.

In 13 instances there was only a systolic murmur. This cannot be satisfactorily explained. It might be conjectured that there is a functional opening between the aorta and pulmonary artery only during systole, influenced perhaps by a large clot in the aneurysmal sac or a peculiar type of tear. Still further Lamplough [28] in 1897 stated that a simple opening between the aorta and a venous trunk without an aneurysm probably would not produce a murmur.

*Thrill.* A thrill was present in 44 of the 68 patients and was described as a purring, harsh, or an intense tremor. It was systolic alone in 16 of these (36 per cent), continuous in nine (21 per cent), and systolic and diastolic in three (7 per cent). In 11 instances (25 per cent) a thrill was present but the phase of the cardiac cycle in which it occurred was not described. In five cases (11 per cent) it was stated that no thrill was observed. In the remaining 24 instances no mention was made of a thrill.

Holman [21] in his monograph on arteriovenous aneurysm has explained the thrill upon the same basis as that mentioned above in connection with the murmur, i.e., the setting into vibration of the vessel walls as well as the edges of the aneurysmal orifice by the eddies produced at the region of the rent between the aorta and the pulmonary artery.

*The Immediate Fall in Blood Pressure and the Ensuing Collapsing Pulse.* At the onset of the fistulous communication between the two vessels, the blood pressure, among other factors, undergoes a marked change in its character. Reimann [25] states that the systolic as well as the diastolic pressure drops to an almost imperceptible level. An adequate arterial pressure in the circulation under conditions of normality depends upon several factors: (1) the cardiac output, (2) peripheral resistance in the arteriolar and capillary beds, (3) the total capacity of the circulatory tree determined by the contraction or dilation of the vessels, (4) the total circulating blood volume,[21] and (5) viscosity of the blood. Since the alteration of any one of these factors may change the blood pressure, it is obvious that a situation such as an abnormal communication between the aorta and pulmonary artery will bring about a marked deviation of the pressure from its normal level. The abnormal fistulous aperture resulting from the rupture causes a shunt of the arterial blood and thus, by depriving the capillaries of the usual volume of circulating blood, causes a decrease in the peripheral resistance and a proportional fall in the blood pressure. As Holman [21] has stated, "obeying the law of hydraulics that flowing water seeks the line of least resistance, it is inevitable that a considerable volume of blood will be diverted from the general circulation with its high capillary resistance into the shorter circuit with

its markedly lower fistulous resistance." This condition, he continues, is similar to blood loss from excessive hemorrhage, except that here the bleeding is into the pulmonary artery.

It appears logical to assume that the degree of fall in the blood pressure depends upon two factors: (1) the size of the fistula, and (2) the amount of blood passing through the new orifice from the aortic to the pulmonary channel. Naturally, the latter is directly proportional to the former. Sudden, severe laceration resulting in a large opening will increase both factors so that the blood pressure within the arterial (aortic) stream will be markedly decreased; whereas in slow erosion with a resulting small communication a slight fall would ensue. It likewise seems logical to assume that the increased amount of blood being shunted will raise the pressure in the pulmonary system of vessels, and this plus the fact that an equal amount of venous blood will be retarded in the right ventricle, will result in decompensation and evidence of congestive failure. With a sudden shunting of blood the hemodynamics favoring a marked drop in systemic blood pressure may reach shock levels before readjustment can come into play.

To overcome this fall in blood pressure there occurs a gradual degree of compensation which may appear at once or after a short intervening period. This compensation is brought about by an increase in vigor of cardiac contractions as well as an increased cardiac rate, and by an increase in the total blood volume.[21] Due to these combined factors the systolic pressure begins to rise and reaches the level of its former height or may progress higher.[25] The diastolic pressure remains at a low level and does not rise, or if it does, only slightly and to a negligible degree in comparison to the systolic. In several experiments with artificial fistulae Holman [21] found that in every case of patent ductus arteriosus the diastolic pressure remained permanently lowered, whereas the systolic pressure was eventually restored to a normal degree.

As regards the increase in total blood volume, Holman [21] has stated that "The larger the fistula the greater will be the volume of blood flowing through the fistula. Necessarily, the compensatory changes to neutralize this loss of blood to the rest of the body must be proportional to the amount of blood so diverted, and one is justified in assuming that the increase in total volume of blood is equal to the amount of blood short circuited through the fistula."

The ensuing wide variance in the systolic and diastolic pressures after the above compensatory mechanisms have occurred, results in a high pulse pressure in the arterial stream which at the periphery produces the hydrodynamic phenomena found in aortic regurgitation such as water hammer or collapsing pulse, Duroziez's sign, increased venous pressure, capillary pulsation, and increased cardiac rate. With this also is the Hill and Rowlands sign (a large difference in blood pressure in arm and leg).[11] This latter was particularly noticeable in one of Porter's cases in which the blood pressure was 105 mm. Hg systolic and 30 mm. diastolic in the arm, over 140 mm.

systolic and 35 mm. diastolic in the leg. In one instance at Charity Hospital (Case 2) a difference of only 122 mm. systolic and 40 mm. diastolic in the right arm and 145 mm. systolic and 60 mm. diastolic in the right leg was observed.

The pulse was described as collapsing, large, or jerking—all probably referring to the typical pulse as described by Corrigan—in 59 per cent of cases in which the pulse was reported. There was a definite statement that no collapsing pulse was observed in two of the patients (4 per cent). In the remaining reports, the pulse was described variously as irregular, rapid, or feeble.

*Pallor and Cyanosis.* In the majority of cases reported in the literature a mention was made of the lividity or cyanosis of the patient, usually in connection with the face, lips, mucous membranes, or finger tips. This factor was conspicuous in 27 instances (66 per cent). A pale face with lividity of the lips was noticed in five (12 per cent). Marked pallor was noted in six instances (15 per cent). Jaundice of the face, sclera, and mucous membranes was mentioned as an outstanding sign in two cases. It was stated in one instance that no change was observed. In the remaining 27 cases no mention of the appearance of the patient was made.

The explanation of the pallor in approximately 15 per cent of cases is explained upon the shunt of blood from the aortic circulation to the pulmonic. Due to the lessened amount of circulatory arterial blood reaching the periphery, there results a marked relative anemia of the parts involved. According to Burwell, Eppinger and Gross,[5, 12] there is a great amount of blood shunted from the aorta to the pulmonary artery in the patent ductus arteriosus. These workers in studying cases at the time of ligation of the duct of Botalli ascertained that the amount of blood short circuited through the pulmonary system amounted to between 4 to 19 liters per minute or from 45 to 75 per cent of all of the blood that leaves the left ventricle. This blood returns to the left ventricle via the pulmonary artery and veins and thus is of no physiologic value. "This means that the left ventricle puts out 2 to 4 times the volume expelled by the right." Experiments by these same workers on dogs in which the subclavian artery was anastomosed to the pulmonary artery showed an increase in the amount of blood entering the pulmonary circuit to over double that observed when the circulation was intact. Under normal conditions the rate of blood flow in the pulmonary circuit in one case quoted by Eppinger et al.[12] was 2.31 liters per minute, and after the communication was established, this increased to 5.47 liters per minute. At the same time the peripheral flow decreased from a level of 2.31 liters per minute to 1.30 liters per minute. These factors reveal that an extremely large amount of blood passes through the site of the rupture of the aneurysm into the pulmonary artery. Since 45 to 75 per cent of the blood is shunted through the pulmonary circuit and thence to the left ventricle and then reshunted etc., ad infinitum, the periphery must suffer this loss until compensation can be established in one of the ways mentioned above, i.e., increased cardiac rate,

increased total volume, and increased cardiac output. Holman [21] likewise states that "when the flow is directed from aorta to pulmonary artery, a considerable volume of aerated blood is deflected from the systemic circulation, the effect of such deflection manifesting itself in a marked pallor of the skin." The net result, therefore, is pallor from an insufficient supply of aerated blood.

Since in the patent ductus, as would be the case in a communication through a ruptured aneurysm of the transverse and descending aorta, the deflection occurs distally to the subclavians and carotids, the pallor would be of the lower extremities primarily. If, however, the shunt occurred from the ascending or transverse aorta to the pulmonary artery proximal to the branching of the subclavian or carotids from the aorta, there would be a deficiency of blood reaching all parts. The site of the aneurysm in 85 per cent of cases was of the ascending aorta. The above argument would indicate that these should show a diffuse pallor. However, only 15 per cent of all reported cases had this as a prominent sign.

The explanation of the *cyanosis* (*66 per cent of cases*) may be upon the basis of two factors: (1) Pulmonary edema, and (2) sudden decompensation of the heart. In the former consideration one may postulate that the increased burden thrown upon the pulmonary circulation by the shunting of blood under high pressure from the aortic stream and this load added to that already emerging from the right ventricle, would so congest the pulmonary circuit that insufficient oxygenation would result. A picture of pulmonary edema simulating backward failure would appear. Eppinger, Burwell and Gross [12] state that pulmonary congestion is a constant finding in patients with patent ductus. As mentioned above, Burwell et al.[5, 12] showed clinically and experimentally that approximately 45 to 75 per cent of the blood emerging from the left ventricle was thrown into the pulmonary circulation through the patent ductus arteriosus or through experimental fistulae.

As Holman [21] states with regard to the interventricular septum defect, the "congestion has the appearance of so-called passive congestion, but it is evident that in these cases it followed not a passive but an active state of the circulation." This of course applies to the condition under discussion as well. This excessive burden added to that already present in the circuit would be more than that with which the left heart could cope at once and the edema would increase. Concomitantly the shunting blood would cause some dilatation of the pulmonary artery and quite probably some involvement of the pulmonary valves. Holman in his cases found the pulmonary artery to be dilated invariably. With this valvular involvement, a regurgitation of blood into the right ventricle results. Later right ventricular congestive failure may ensue. Holman states that in the patent ductus a dilated left heart is also characteristic. With the resulting cardiac decompensation cyanosis is the end result.

The possibility of a retrograde flow of unoxygenated blood from the pulmonary artery into the aerated aortic circulation is not to be overlooked

as a cause of the cyanosis. Unless some factor comes into play to lower the pressure within the aorta or increase that within the pulmonary artery, there is sufficient drive within the former vessel to make this hardly a factor in the production of cyanosis. Holman [21] does, however, postulate such a factor in the patent ductus arteriosus upon substantial evidence of case records and experiments. He believes that such a retrograde flow is not only possible but a fact in those instances in which there is some hypertrophy of the right ventricle. This hypertrophy, he states, so increases the pressure within the pulmonic circuit that it rises above that within the aorta. With such circumstances existing the flow of blood is then from the pulmonary artery into the aorta, thus bringing about a state of affairs, which as he suggests should be termed more accurately a "venoarterial fistula" rather than an "arteriovenous fistula." Such mixing of unoxygenated blood with the peripheral circulation could obviously cause the cyanosis observed.

Experiments by Levy and Blalock [31] and those by Eppinger et al.,[12] however, have shown conclusively that the flow of blood in the patent ductus is from the aorta to the pulmonary artery and that there is no flow from the pulmonary artery into the aorta. These investigators have found that even in the case of a fistulous connection between the two vessels in question, in which a powerful left ventricle is pumping large quantities of blood through the aperture into the pulmonary circuit, the pressure in the latter does not approach that within the aorta. As Eppinger et al.[12] state, "the obvious explanation is that the resistance in the lungs is much less than in the periphery."

Burwell et al.[12] do admit that one set of circumstances may exist that will so raise the pressure in the pulmonary artery as to exceed that in the aorta. This factor is back pressure resulting from some obstruction distal to the communication such as a failing left ventricle or some form of pulmonary disease. Above we have shown how the development of a failing left ventricle may proceed. We are not of the opinion that this is the causal agent of the cyanosis as evidenced in the patient with an aneurysm of the aorta rupturing into the pulmonary artery.

Taylor [54] has suggested that within an aneurysmal sac there is probably a decrease in pressure in relation to the parts of the vessel proximal and distal to the sac. If this be true, then there may exist some retrograde flow upon this basis. With the existence of an hypertrophied right ventricle (as suggested by Holman) in addition to the observations of Taylor, i.e., a proportional increase of pressure on one side with a proportional decrease on the other, such retrograde flow is possible and a cyanosis is explainable upon this basis. However, no work has been done along these lines to refute or substantiate this hypothesis.

*Edema.* In almost every instance there was edema, usually beginning in the lower extremities and gradually ascending to the scrotum, sacrolumbar region, abdomen, chest, face, and upper extremities until a marked generalized edema or anasarca resulted. In 22 cases this anasarca developed almost at

once or over a very short period of time (42 per cent). In the remaining cases in which edema was observed, it was limited to the lower extremities, face, or abdomen (table 4). As Thurman [55] stated as early as 1840, when a communication occurs between the aorta and the pulmonary artery "the whole body is the seat of dropsical effusion" as compared with the lower body edema in an arteriovenous aneurysm between the aorta and the inferior cava and an upper body edema in a case of communication between the superior vena cava and the aorta.

Recent work as described by Porter [40] indicates that the direction of the blood flow into the pulmonary artery is important in the production of such right ventricular stress. If the communication is such that the shunted stream enters in the direction of blood flow through the pulmonary artery, then we would anticipate fewer immediate symptoms of right heart failure. Pulmonary congestion with some cyanosis and dyspnea (q.v.) would be the salient feature. However, if the shunt is such that the stream hits the flowing pulmonary circuit at a right angle, there would occur a splitting of the entering stream so that almost an equal amount would go in both directions, i.e., into the pulmonary circuit away from and toward the right ventricle, thus producing an increase of load on the right ventricle. In the third possibility, the blood flow may be directly toward the right ventricle which would at once overburden the right heart and possibly result in immediate decompensation. One must keep in mind also that, as a certain additional amount of blood enters the pulmonary artery, regardless of the direction of flow, the volume in the pulmonary circuit must increase, and the pulmonary vascular bed and right side of the heart must undergo the necessary volume changes to cope with the additional volume of blood. Until the right ventricle fails, the increase in blood volume in the pulmonary circuit is taken care of by the pulmonary vascular bed.[12]

*Dyspnea.* Sixty-seven per cent of the patients reported had dyspnea without orthopnea. In 33 per cent orthopnea was a primary complaint. Those with dyspnea progressed rapidly to an orthopnea terminally. The explanation of this symptom is set forth by Porter.[40] He attributes the increasing breathlessness to the Hering-Breuer reflex. As he implies, the fistulous communication between the two vessels increases the amount of blood in the pulmonary circuit and thus causes an engorgement of the pulmonary vessels. Since the reflex is dependent upon changes in tension within the lung parenchyma, the added amount of inflowing blood produces the necessary stimulus, which results in dyspnea. One may also postulate that the congestion within the lungs interferes with oxygenation so that the respiratory center is stimulated. However the Hering-Breuer reflex appears to be the more important. When congestive heart failure sets in, other factors said to cause dyspnea come into play.

*Cough and Expectoration.* There was present a cough in 93 per cent of cases but with hemoptysis in only 33 per cent. This is explainable upon the

basis of engorgement and congestion of the lungs as well as possible pressure by the aneurysm upon the recurrent laryngeal nerve and bronchi.

*Roentgenography.* Roentgenographic studies were mentioned in only 13 reports, all recent. The aortic knob was enlarged in 10 patients, whereas in three no noticeable change was observed. The usual picture is that of an aneurysmal sac of varying size extending to the left of the sternum. There is usually an associated dilatation of the pulmonary conus. This latter state was present in eight of the 13 reported cases. In the other five, no mention was made of the nature of the conus. In 10 instances, the heart was enlarged, varying from "slight enlargement" to "enlargement in all directions." In most instances the heart was diffusely enlarged. This was true in the two patients seen at Charity Hospital. In these two patients fluoroscopic examination showed increased pulsations of the pulmonary vessel and pulmonary conus. Diodrast studies in one patient showed the fistula and enlarged pulmonary conus and vessels. These latter two types of roentgenographic observations proved to be of great value in the detection of the fistula.

*Electrocardiography.* Electrocardiographic studies were reported in six cases. They were non-specific and showed no points of similarity. In one of Porter's [40] patients, there was a right axis deviation, due probably to right ventricular strain resulting from over burdening of that chamber. There was left axis deviation in another of his patients. Mallory [33] reported a low take-off of the ST segment in Leads I and IV and an elevation of the ST segment in Lead III. There was also some inversion of $T_1$, $T_2$, and $T_3$. No axis deviation was noted. In one patient (Number 1) at Charity Hospital there was evidence of low T-wave in Leads I and II, and a low and notched T in Lead IVF. There was beginning right axis deviation with a depression of the $ST_2$ and $ST_3$ (possibly due to digitalis). In two of Porter's cases [40] and in one at Charity Hospital, there was evidence of sinus tachycardia. In the other patient at Charity Hospital the electrocardiogram was normal. Until further study is made with regard to the electrocardiographic changes in this condition, nothing can be stated as to definite configuration. However, from the evidence at hand, one can draw certain conclusions: (1) There may be a right axis deviation or a normal electrical axis, (2) sinus tachycardia, and (3) some change in the T-waves (lowerings, inversions, or diaphasicity) in Lead I or all three leads, with a low T-wave in Lead IVF.

## The Clinical Picture

*History.* In 1840 Thurman [55] set down definite diagnostic criteria by which a diagnosis of a communication between an aneurysm of the aorta and the great vessels of the mediastinum could be made. His principles were:

"1.) General signs: Severe and rapidly advancing anasarca of such portions of the body as are below, or the venous system of which is distal to, the

varicose orifice. When the varicose aneurysm is between the aorta and the inferior vena cava, the legs, scrotum, and lower half of the body; when between the ascending aorta and superior vena cava the arms, face and the upper half of the body; and when between the ascending aorta and one of the right or left cavities of the heart or *pulmonary artery,* the whole body is the seat of dropsical effusion.

"2.) Livor of the face particularly, but, likewise in a less degree of all such portions of the body as are below the varicose opening.

"3.) A distended and even varicose condition of the subcutaneous veins distal to the orifice.

"4.) Dyspnea, often amounting to orthopnea, and terminating in apnea.

"5.) Cough with expectoration, especially if the sputa be bloody.

"6.) Remarkable jerking and in some cases very feeble pulse.

"7.) Emaciation, debility, loss of muscular power, deficient animal heat, and sensorial disturbances, may be looked upon as somewhat less frequent than certain signs.

"8.) Physical signs: A superficial, harsh murmur and peculiarly intense sawing or blowing sound, accompanied by an equally marked and purring tremor, heard over the varicose orifice and in the current circulation beyond it; this sound is continuous, but is loudest during systole, less loud during diastole, and still less so during the interval." [55]

In 1839 Hope [22] in his classic, "Diseases of the Heart," set forth certain signs which he considered to be pathognomonic:

"1.) A very loud, superficial, sawing murmur prolonged continuously over the first and second sounds (probably weaker during the period of repose) and loudest along the tract of the pulmonary artery.

"2.) A purring tremor in the pulmonary artery, in the interspaces between the second and third ribs.

"3.) Second sound weakened at the clavicles.

"General signs:

"1.) Jerking pulse. 2.) Great, rapid, and universal dropsy. 3). A livid venous tint. 4.) The circumstances of the symptoms having followed an effort." [22]

Pepper and Griffith [38] in 1890, commenting on varicose aneurysms of the thorax, set forth diagnostic criteria which conform closely to those mentioned by the above observers.

Clarke [7] in 1900 upon the basis of three cases added palpitation immediately following the onset of symptoms as an important complaint. He mentioned the possibility of an enlarged heart, especially the right ventricle, and also observed that the pulse, although usually of the Corrigan type, did not necessarily conform to this. In his patients there was a certain amount of euphoria. He was impressed by the oliguria present and

mentions this as an important diagnostic finding. This has been observed in only three of the cases in the literature.

Hill and Rowlands [11] in 1922 showed that there was a difference in the blood pressure in aortic regurgitation between the arms and legs (the latter being greater than the former). In 1923 Lewis and Drury [32] showed clinically that in arteriovenous aneurysms there was likewise present the Hill-Rowlands' sign together with other manifestations of aortic regurgitation: lowered diastolic pressure, waterhammer pulse, capillary pulsation, increased cardiac rate, etc. (The hydrodynamic phenomenon of aortic regurgitation.)

A personal communication from William Porter [40] indicates that he recently has had three cases, two of which he has diagnosed ante mortem and upon these cases he has constructed a clinical syndrome. This syndrome conforms essentially to the fundamentals set forth by Hope and Thurman 100 years ago.

*Course.* That such a communication between the aorta and the pulmonary artery is perfectly compatible with life (for a certain length of time at least) is understandable, when one considers that the relationship only sets up an "arterio-arterial" aneurysm in which the pressure upon the arterial side is sufficient to prevent any regurgitation of the reduced hemoglobin into the aortic circuit. Although Holman [21] believes that there is a possibility of such a retrograde flow of blood from the pulmonary artery into the aorta in the condition of patent ductus arteriosus, the recent experimental work of Levy and Blalock [31] and of Eppinger et al.[5, 12] has proved conclusively that this does not occur and that the flow is always from the aorta into the pulmonary artery. Rupture of an aneurysm under any other circumstances results in early death.

It is true that a large number of cases did die at once or within a few hours following the rupture, but the majority of patients had a long survival. Clerc [8] reports a case with a four year survival after evidence of rupture. This, however, is a rare instance and some question may be placed upon the actual onset of symptoms. The average duration of life is between six weeks and four months.

Naturally this duration depends upon the type of rupture, the size of the orifice, the amount of blood flowing through the communication and the ability of the patient to compensate. When the rupture is sudden and the laceration great with a resulting wide fissure, the amount of blood suddenly poured into the pulmonary circuit will over burden the latter and the heart, and overwhelming symptoms and death will occur in a short period of time. On the other hand, if a small opening is produced, though sudden, only a small amount of blood is suffused into the pulmonary stream so that life may continue for a prolonged length of time. As Eppinger et al.[12] have stated: "Adjustment of the circulation (in a patent ductus) may be made by an increase in the output of the left ventricle. If this is not sufficient to compensate completely for the leak there may be, in addition, a diminution in the

blood flow to the periphery." On the other hand one might assume that the increased output of the left ventricle in the case of ruptured aneurysm might only serve to increase the pulmonary congestion.

*Clinical Picture.* Characteristically, when the vessel walls break through, whether suddenly or through thinning and erosion, there is subjectively observed a severe pain in the left chest, with radiation to the interscapular region, head, neck, or epigastrium; a certain degree of constriction or tightness is felt within the chest, or a sense of something giving away in the precordial area. Usually this pain or constriction follows some physical exertion or frequently some illness of long duration. The characteristic picture is that of sudden onset with severe precordial pain and dyspnea following some strain as lifting a heavy load, vomiting, or paroxysms of coughing.

Rapid and progressive edema next follows, frequently beginning in the lower extremities or upper extremities and progressing until the whole body is the "seat of dropsical effusion."

When the patient is seen, the first impression is that of congestive failure with marked dyspnea, anxious facies, cyanosis, edema of limited areas or complete anasarca. There may be a state of euphoria as reported in three cases. There may be oliguria. Pallor may be present instead of cyanosis but when the former occurs it is usually limited to the upper extremities and face. The extremities are frequently cold to touch and the patient will be shaken by paroxysms of coughing with expectoration or hemoptysis. He may complain of severe degrees of palpitation.

Physical examination reveals an acutely ill patient who is exerting every effort to breathe. The lips, face and extremities are extremely pale or cyanotic. There is a progressive edema of the extremities and trunk which within a few days or hours may attain the proportions of complete anasarca. Palpation of the chest will reveal a purring or intense thrill, systolic or diastolic or both, to the left of the sternum in the second or third left interspaces in the region of the pulmonary area. Percussion will give all indications of a mass beneath or to the left of the sternum with an increase in cardiac dullness to the right. Upon auscultation a loud, humming, machine-like murmur is heard in the region left of the sternum extending from the second to the third interspaces and being continuous throughout the cardiac cycle. It is crescendo-decrescendo in character.

The hydrodynamic phenomenon of aortic regurgitation is manifest with its collapsing or Corrigan type of pulse, Duroziez's sign, capillary pulsation, increased cardiac rate, etc.

Roentgen-ray will reveal the presence of aneurysm of the aorta and in addition, marked change in the configuration of the heart boundaries. The electrocardiogram will often show some axis deviation, a sinus tachycardia, and some change in the T-wave.

Clinically, the course will continue as mentioned above along lines depending upon size of the aperture, the type of rupture, and the amount of blood passing through the orifice. The edema may subside as compensation ensues,

but eventually it will again become progressive until anasarca is predominant. Cough and expectoration will increase and hemoptysis, if not already present, will soon appear as congestion in the lungs becomes more prominent. Eventually all symptoms become more manifest until death terminates the picture in complete circulatory collapse.

## The Syndrome

The criteria for the syndrome may be summarized as follows: From the tables as given above, and from the incidence of occurrence of the major and outstanding symptoms as presented in 81 cases recorded in the literature, and two cases observed at Charity Hospital the principal diagnostic criteria have been drawn. With these factors at hand, a syndrome has been compiled which is composed of the following essential points:

*History:* Sudden onset with severe stabbing pain or a sense of oppression in the precordial area with or without radiation, usually following physical exertion, and succeeded by marked and increasing dyspnea.

*Subjective Signs:* (1) Marked and increasing shortness of breath. (2) Progressive swelling of the lower extremities and trunk. (3) Rasping cough with expectoration or hemoptysis. (4) Bluish discoloration of the face and extremities. Pallor may be the alternative.

*Objective Signs:* (1) An intense thrill in the second to third left interspace occurring during systole or continuance throughout the cardiac cycle. (2) Humming "machine-like" murmur, heard best to the left of the sternum in the second or third interspaces, continuous throughout the systolic and diastolic phase and crescendo-decrescendo in character, being more intense during systole. (This murmur resembles that heard in a patent ductus Botalli.) (3) Evidence of aneurysm of the aorta. (4) Marked and increasing dyspnea usually reaching the extent of orthopnea. (5) Cyanosis of the lips, face, or extremities, or marked pallor of the same areas. (6) Edema of the lower extremities and trunk progressing to anasarca. (7) The hemodynamic phenomena of aortic regurgitation (Corrigan's pulse, increased cardiac rate, capillary pulsation, Duroziez's sign, etc.). (8) Roentgenographic evidence of aneurysmal dilatation of the aorta, prominent and enlarged pulmonary conus, and probable enlargement of the heart. (9) Electrocardiographic indications of a non-specific character but usually indicative of a sinus tachycardia, right axis deviation, and lowering, inversion, or diaphasicity of the T-waves in the standard and precordial (IVF) leads. These findings become even more significant if the patient had been studied previously and was known to have been free of the cardiovascular phenomena described above.

## Case Reports

*Case 1.* U. H., a negro female, aged 39, was readmitted to the Charity Hospital of Louisiana on July 27, 1941 and died on October 27, 1941. She had previously

been treated in 1932 for a gonococcal salpingitis at which time no symptoms referable to the thorax were noticed.

Her complaint on entry was sudden onset of pain two months before in the left chest beginning in the precordial area and radiating down into the left flank. This pain was recurring and intermittent, being precipitated by exertion, as climbing stairs, and lasting 15 minutes. The pain was described as sharp and stabbing. Soon

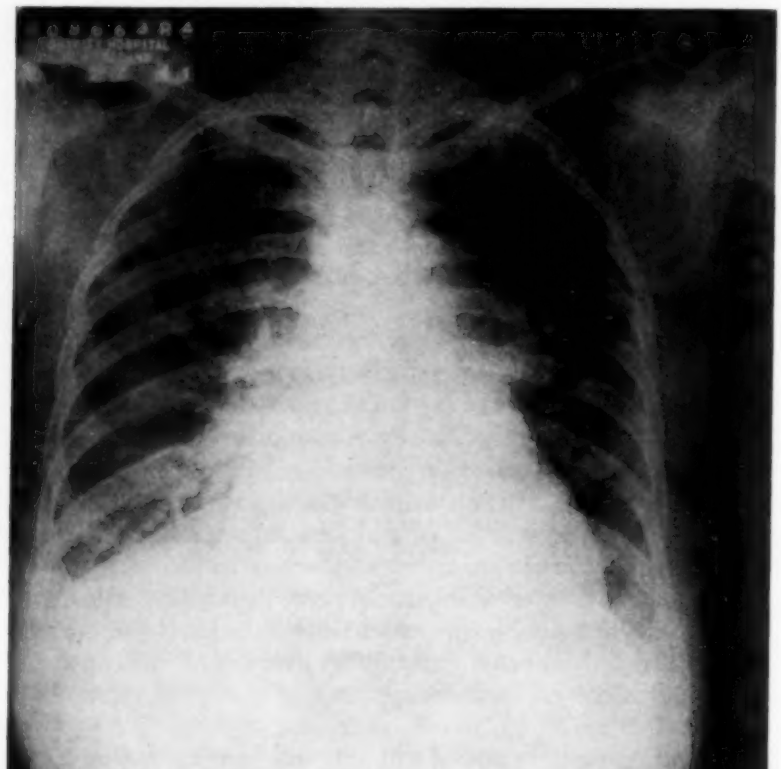

FIG. 1. Case 1. Roentgen-ray shows passive congestion of the lung fields. The heart is diffusely enlarged. Large aneurysm is present on the arch of the aorta.

after the onset of pain, the patient noticed palpitation and dyspnea which were increased by exertion, and some edema of the lower extremities. Three weeks before ascites had been observed. She had been unable to "hold anything on her stomach" since onset, and had vomited excessively. There was some weakness in the epigastrium and a precordial fullness. A "cold" and cough developed about the time of the onset and appeared to have initiated the first attack. The cough was productive of blood upon one occasion. All these symptoms had progressed since onset.

Examination upon entry revealed a well developed, negro female about 40 years of age who did not appear acutely ill but was propped up in bed in order to breathe. The examination was essentially negative except for pale conjunctivae and the findings in the chest. Over the lung fields moist inspiratory and expiratory râles were heard with some diminution of the intensity of breath sounds at posterior bases. The heart was enlarged; the apex beat was felt in the anterior axillary line in the seventh interspace. A diffuse pulsation with a marked thrill was felt over the precordial area, especially intense in the second and third left interspaces. A systolic murmur was heard at all valve areas especially loud at the pulmonic area. The pulmonic second sound was greater than the aortic second. These sounds were transmitted throughout the thorax both anteriorly and posteriorly. The murmur at the pulmonic area was described as harsh and loud. The abdomen was moderately distended but no shifting dullness was elicited. The liver was palpable on the right to a level slightly below the umbilicus. There was some tenderness in this area to deep palpation. The blood pressure was 144 mm. Hg systolic and 40 mm. diastolic and the pulse 80 per minute. The pulse was described as "pistol shot" in character.

*Course in Hospital:* Two days after admission, there was observed a diastolic pulmonary murmur in addition to the systolic murmur. It was described as long and low pitched. There was no enlargement of cardiac dullness. Post sacral and lower

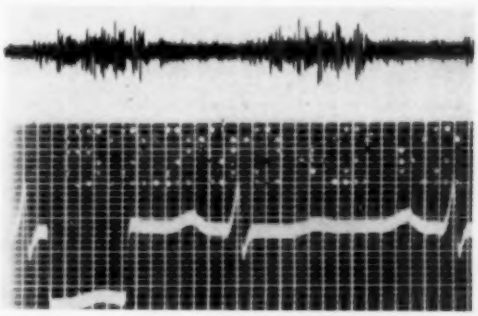

FIG. 2. Case 1. Sound tracing taken over the pulmonic valve area, showing a murmur which is continuous throughout the cardiac cycle with systolic accentuation.

extremity edema was noted and there was some evidence of fluid in the abdomen. The Wassermann test was strongly positive. Roentgenogram of the chest revealed considerable passive congestion, enlargement of the heart, and an aneurysm of the arch of the aorta. Upon auscultation a week later, the systolic and diastolic murmurs at the pulmonic area were found to be a continuous hum in the second and third left interspaces, extending through both phases and being crescendo-decrescendo in nature. A harsh systolic and diastolic murmur was heard at apex. Fluoroscopy at that time revealed right and left ventricular enlargement with prominence of the aortic knob and pulmonary artery with marked pulsation of the left main branch of the pulmonary artery. Some compression of the pulmonary artery was postulated. Fluoroscopy indicated that an aneurysm of the left pulmonary branch might be present. On August 18, 1941 "diodrast" injections were done. These showed marked enlargement of the pulmonary artery. Venous pressure at this time was 210 mm. of water, and circulation time (arm to tongue) was 30 seconds. The patient's symptoms and edema improved under digitalis and potassium iodide therapy, but, due to gastrointestinal disturbances they were discontinued. At this time the tentative suggestion was offered that there might exist a connection between the aorta and the right heart or pulmonary artery, giving symptoms simulating a patent ductus arteriosus. For several days the patient coughed up small flecks of blood and frequently vomited.

A month after admission, the pitting edema of the ankles with some ascites was again noted, and two days later a puffiness of the face developed. Venous pressure was 280 on October 1, 1941. From that date on, the patient's condition steadily declined with increasing dropsy, dyspnea, frequent watery stools, and increased signs of failure. This progressed to termination on October 27, 1941 with signs of general cardiac failure.

The electrocardiogram showed low T-waves in all leads with a slightly diphasic T-wave in Lead IVF. The rate was 120 per minute. On August 7, 1941 a noticeable depression in the ST segments in Leads II and III was observed, which was probably due to digitalis. The T-wave in Lead IVF was low and notched. At this time, sound records were taken which showed a systolic murmur loudest at the pulmonic area with a probable soft dimuendo diastolic murmur in the same area.

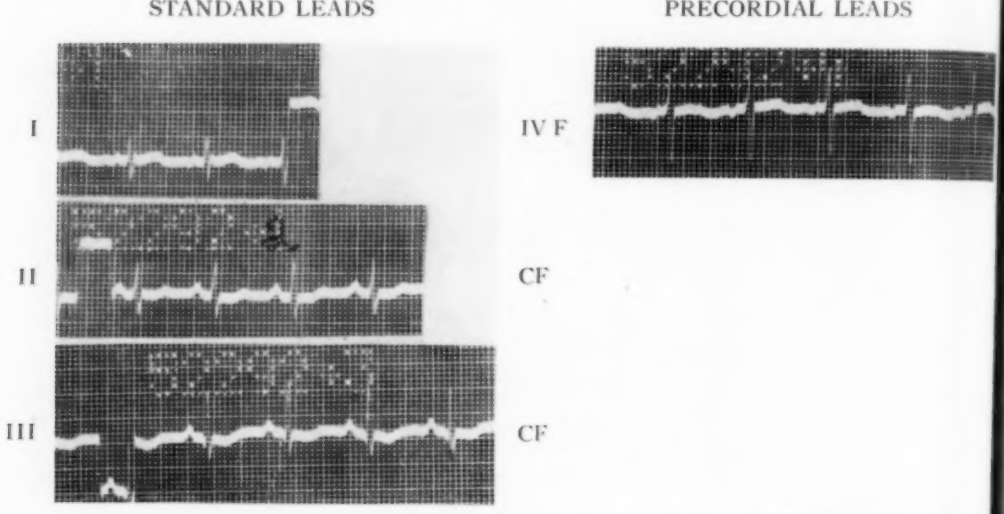


FIG. 3. Case 1. Electrocardiographic tracings show a sinus tachycardia (rate 120 per minute), a depression of the ST segments in Leads II and III (probably due to digitalis), and a low and notched T-wave in Lead IVF.

*Laboratory:* Red blood cells on admission were 5.4 million, and white blood cells 8000 which decreased to 5.1 million and 3000 respectively August 30. Specific gravity of the urine remained between 1.017 and 1.025 with albumin ranging from 1 to 4 plus. Many white blood cells and casts were found in the urine. The urea nitrogen varied from 21 to 44 mg. per 100 c.c. of plasma. The clinical diagnosis was communication between an aortic aneurysm and the pulmonary artery.

The findings at autopsy performed by Dr. Wm. H. Harris of the Department of Pathology at Tulane University and Charity Hospital, were as follows: A colored female weighing 115 pounds who showed marked edema of the extremities and over the sacral area. There was some jaundice of the sclerae, conjunctivae, and mucous membranes. Both pericardial and peritoneal cavities contained a large amount of fluid. The heart was enlarged, being more so in the right auricle and right ventricle. The pulmonary artery was markedly dilated at its point of origin from the right ventricle. The right and left branches of the pulmonary artery were also dilated.

A large saccular aneurysm was found on the transverse portion of the aorta in the region of the origin of the left subclavian artery. This sac was in communication with the left main branch of the pulmonary artery through an elliptical opening

measuring 6 mm. in diameter. This aperture was about 2 cm. beyond the bifurcation of the main pulmonary artery. The edges of the communication were smooth and rounded.

The detailed pathologic findings will be discussed by Dr. Schattenburg and Dr. W. H. Harris of the Department in another article.

*Case 2.* N. R., a colored male 40 years of age, was admitted to the Charity Hospital of Louisiana on January 2, 1942 and died January 3, 1942. His chief com-

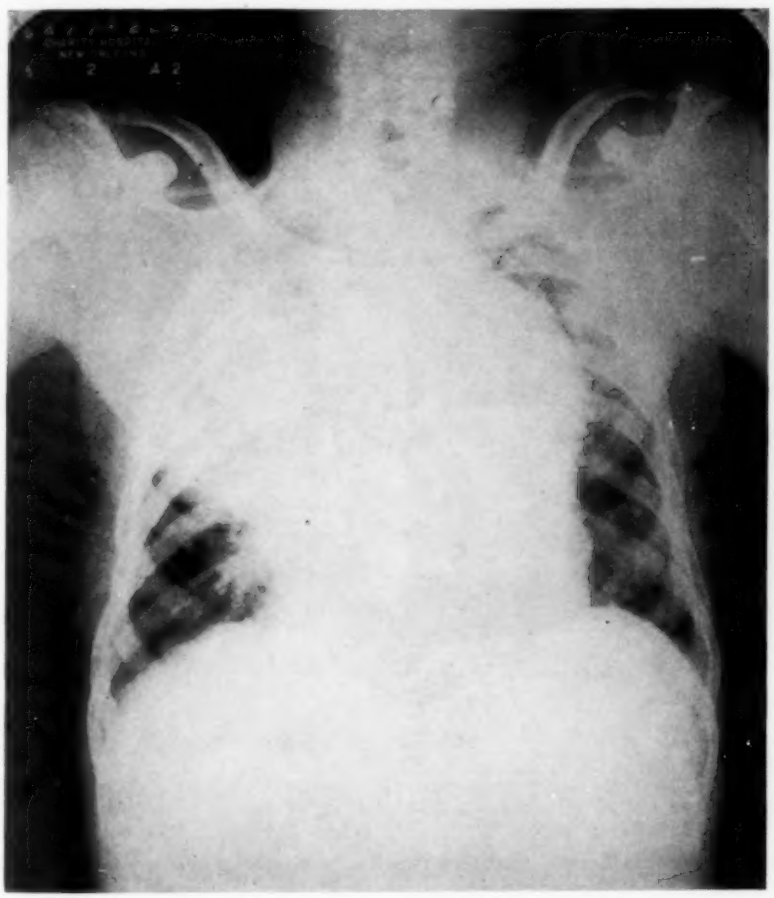

FIG. 4. Case 2. Roentgen-ray showing marked enlargement of the heart with enlargement of the upper mediastinal shadow. A large saccular aneurysm of the aorta is present. There is some congestion of the lung fields.

plaint was chronic cough of three months' duration, and dyspnea, orthopnea, and expectoration of five days' duration. The patient stated that he had been perfectly well until three months previously when he began to have a non-productive cough which continued without any other symptoms until five days before admission when he was riding on a bus and suddenly felt a "snap" in his chest. Associated with this was an acute pain under the left shoulder and marked increasing dyspnea to orthopnea. His cough became productive and on the day of admission he noted that his sputum was blood-tinged. When he entered the hospital, he was in frank heart failure.

The review of systems was essentially negative. There was a history of a weight loss of 18 pounds in the past month, and of occasional dizzy spells with "spots before the eyes" during this same interval. His past history revealed a "double pneumonia" 18 years before and a positive syphilitic history 10 years prior to admission. The syphilis had been inadequately treated.

Physical examination at the time of admission revealed a well developed, fairly well nourished colored male who showed evidence of severe orthopnea. The blood pressure was 124 mm. Hg systolic and 40 mm. diastolic in the left arm, 122 mm. systolic and 40 mm. diastolic in the right arm and 145 mm. systolic and 60 mm. diastolic in the right leg. There was a cough which was productive of a frothy, purulent, blood tinged sputum. Slight cyanosis of the lips and mucous membranes was observed. Inspection of the chest revealed rapid respiration with a slight lag of the left hemithorax.

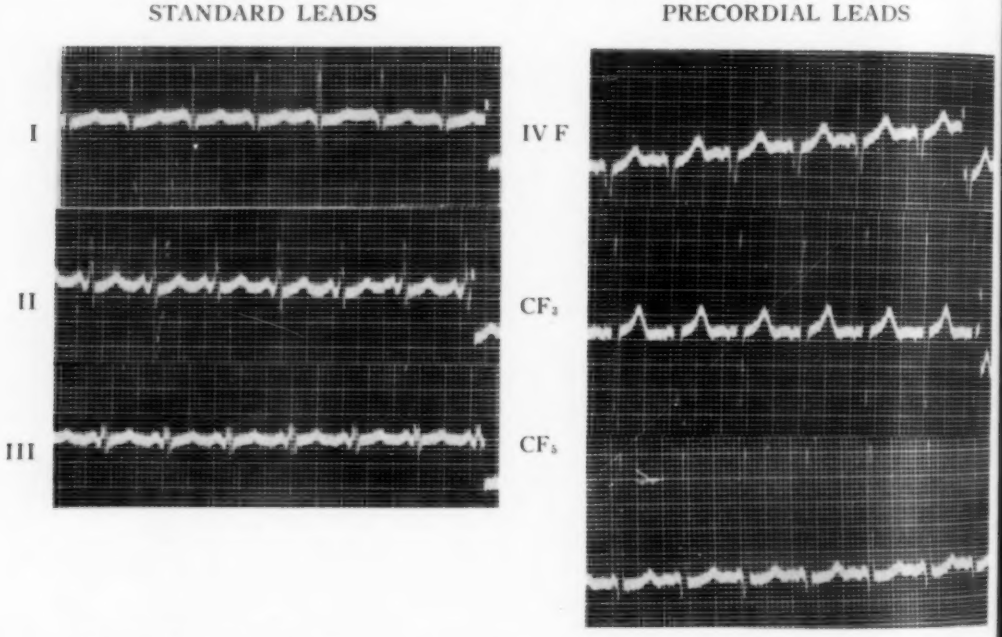


FIG. 5. Case 2. The electrocardiogram is essentially normal. There is a sinus tachycardia of 122 per minute and a slight slurring of the QRS complexes in all leads.

The apex beat could not be distinguished but a pulsating mass was observed in the suprasternal notch. There was a palpable thrill over the whole precordial area but more pronounced in the second left interspace and in the region of the pulmonary valve. This thrill could be felt throughout the cardiac cycle, being accentuated with systole. Percussion of the thorax showed a slight increase in cardiac dullness to the right and in the region of the pulmonary conus and left auricle. Auscultation revealed areas of vesicular breathing with many râles in the upper lobes, especially prominent in the right upper lobe. Inspiratory and expiratory wheezes were heard at the bases. Over the pulmonic valve area, a continuous humming machine-like murmur, not unlike that heard in a patent ductus arteriosus, was detected. This murmur was accentuated during systole of the heart. This murmur was transmitted over the whole precordium and up into the neck vessels. No other murmurs were heard at the other valve areas. The radial pulse was rapid, regular, and of the Corrigan type. The remainder of the physical examination was essentially negative, except for a slightly palpable liver. *No ascites or edema of the extremities was observed.*

*Course:* The patient did not respond to measures instituted such as morphine, digitalis, continuous nasal oxygen, etc., but grew steadily worse. He died on January 3, 1942, twelve hours after admission to the hospital.

*The electrocardiogram,* taken at the time of entry, was normal. There was a sinus tachycardia of 122 per minute and a slight slurring of the QRS complexes in all leads.

*Roentgen-ray* showed marked enlargement of the heart, with enlargement of the upper mediastinal shadows. There was evidence of a large saccular aneurysm of the aorta. There was some congestion of the lung fields.

*Laboratory Data:* The circulation time was 25 seconds on the day of admission, and the venous pressure was 260 mm. of water. There was no anemia and the sedimentation rate was normal.

*The clinical diagnosis was:* Aortic syphilitic aneurysm with rupture into the pulmonary artery.

*Autopsy Findings:* The findings at autopsy performed by Dr. Philip Pizzalatto of Charity Hospital were as follows: The body was that of a colored male, weighing approximately 150 pounds. There was no edema of any part of the body. The pericardial cavity was obliterated by firm adhesions. The peritoneal and pleural cavities contained no excessive fluid. There was enlargement of the liver, the organ extending 6 cm. below the costal margin. There was marked cardiac dilatation of both sides of the heart. Approximately 3 cm. above the aortic valves on the ascending aorta there was a large saccular aneurysm, 6 cm. by 3 cm. in size. This aneurysm was filled with a laminated clot. At the inferior angle of the clot, a small aperture (1 cm. by 2 mm. in diameter) with ragged, uneven edges was found opening into the pulmonary artery just at the point of bifurcation. The aneurysm had completely obliterated the left pulmonary artery. The right pulmonary artery was quite dilated.

## Summary

1. The incidence of rupture of an aortic aneurysm into the pulmonary artery is unusually low when one considers the close anatomical relationship between the two vessels and the great frequency of aneurysm of the thoracic aorta. Since the first clinical instance was reported in 1812 by Wells, only 81 have been mentioned in the literature, including 11 museum specimens. This low incidence in the literature as well as the assumed infrequency of the lesion may be explained upon the basis of pin-point communications between the great vessels, oversight on the part of the pathologist when examining the aorta and the pulmonary artery, and failure to appreciate the condition clinically as a syndrome. Over a 30 year period from 1911–1941 only two instances were observed at the Charity Hospital of Louisiana at New Orleans. During this interval there were approximately 1,052,667 admissions with 1393 aneurysms of the aorta. Of these 219 were of the thoracic aorta in which 110 ruptured into various sites with only two rupturing into the pulmonary artery (1.8 per cent of all ruptures).

2. The syndrome of rupture of an aortic aneurysm into the pulmonary artery was accurately described by Hope in his "Diseases of the Heart" in 1839, his conclusions being based on one case (Munro's). His description made over 100 years ago conforms closely to the concept of the condition as understood today.

3. An analysis of the 81 cases occurring in the literature has been made in

an attempt to study the incidence of clinical manifestations which might serve as criteria for future recognition of the syndrome. The disturbed physiology which occurs in the condition of rupture of an aortic aneurysm into the pulmonary artery was also discussed. Some of the more important manifestations were:

(1) In 56 cases a *murmur* was heard in the region of the pulmonic valve. It was a continuous, humming, machine-like murmur in 43 per cent of instances, resembling that heard in a patent ductus arteriosus. It was crescendo-decrescendo in character.

(2) A *thrill* was present in 44 cases, being systolic in 36 per cent and continuous in 21 per cent.

(3) The presence of a Corrigan pulse as well as other hemodynamic phenomena of aortic insufficiency is due to the large shunt of blood from the systemic circulation into the pulmonary circuit. This deprives the peripheral circulation of a large part of its total volume.

(4) *Cyanosis* was observed (extremities, lips, mucous membranes, or total cyanosis) in 78 per cent of instances. Marked pallor was present in 15 per cent.

(5) *Edema* was found to follow cardiac decompensation.

(6) *Roentgenographic* studies were present in only 13 of the cases studied. There was observed enlargement of the aortic knob in 10; of the pulmonary conus in eight instances. The heart was enlarged in 10 of the 13 instances.

(7) The *electrocardiographic* findings recorded in six cases were nonspecific in nature. However, right axis deviation or a normal electrical axis, sinus tachycardia, and some change in the T-waves were observed in the majority of reports.

4. Upon the basis of critical analysis of the 81 cases reported in the literature and two instances occurring at the Charity Hospital, a syndrome of rupture of an aortic aneurysm into the pulmonary artery is formulated:

*History:* Sudden onset with severe stabbing pain or a sense of oppression in the precordial area with or without radiation, usually following physical exertion, and succeeded by marked and increasing dyspnea.

*Subjective Signs:*

(1) Marked and increasing shortness of breath. (2) Progressive swelling of the lower extremities and trunk. (3) Rasping cough with expectoration or hemoptysis. (4) Bluish discoloration of the face and extremities. Pallor may be the alternative.

*Objective Signs:*

(1) An intense thrill in the second to third left interspace occurring during systole or continuous throughout the cardiac cycle. (2) Humming

"machine-like" murmur, heard best to the left of the sternum in the second or third interspaces, continuous throughout the systolic and diastolic phase and crescendo-decrescendo in character, being more intense during systole. (This murmur resembles that heard in a patent ductus Botalli.) (3) Evidence of aneurysm of the aorta. (4) Marked and increasing dyspnea usually reaching the extent of orthopnea. (5) Cyanosis of the lips, face, or extremities, or marked pallor of the same areas. (6) Edema of the lower extremities and trunk progressing to anasarca. (7) The hemodynamic phenomena of aortic regurgitation (Corrigan's pulse, increased cardiac rate, capillary pulsation, Duroziez's sign, etc.). (8) Roentgenographic evidence of aneurysmal dilatation of the aorta, prominent and enlarged pulmonary conus, and probable enlargement of the heart. (9) Electrocardiographic indications of a non-specific character but usually indicative of a sinus tachycardia, right axis deviation, and lowering, inversion, or diaphasicity of the T-waves in the standard and precordial (IVF) leads. These findings become even more significant if the patient had been studied previously and was known to have been free of the cardiovascular phenomena described above.

5. Two cases of rupture of an aortic aneurysm into the pulmonary artery are added to the literature, one occurring in a 39 year old female who survived five months after rupture, and the other in a 40 year old male whose duration of life following rupture was six days. Both instances were recognized and diagnosed correctly prior to death.

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# TRAUMATIC HEART DISEASE: A CLINICAL STUDY OF 250 CASES OF NON-PENETRATING CHEST INJURIES AND THEIR RELATION TO CARDIAC DISABILITY *

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Cardiac damage resulting from chest trauma has been known to occur ever since postmortem examinations became a part of medical investigation. Until recently, however, it was believed that most cases of cardiac damage were fatal, and that they occurred only in severe, penetrating chest injuries. In the past two decades, however, and particularly with the advent of electrocardiography, numerous clinical and experimental studies have demonstrated that many cases of severe cardiac damage, including rupture of the heart, result from non-penetrating chest injuries, although the thoracic cage remains intact without as much as a fractured rib.[3, 4, 5, 6, 8, 9, 13, 14, 15] Thus, out of 152 cases of ruptured heart following non-penetrating injuries to the chest gathered by Bright and Beck [7] only 58 showed evidence of fractured ribs.

These authors reported 23 authentic cases of cardiac contusion collected from the literature in which the cardiac injury did not result in immediate death. Experimentally, the same authors produced a variety of cardiac lesions in 25 dogs, five of which survived. They demonstrated numerous electrocardiographic changes not unlike those seen in man with various stages and degrees of myocardial damage. They state that most of these changes disappeared after a month or so whereas others persisted for a long time. Healing of the cardiac injury is the rule. They conclude from experimental and clinical observations that the vast majority of non-penetrating wounds of the heart are not recognized clinically and do not receive the correct diagnosis.

Erik Warburg,[16] in reviewing 225 substantiated cases of non-penetrating injuries to the heart, met with a variety of arrhythmias, including auricular flutter and fibrillation, as well as transient and permanent heart block. He describes cases of traumatic coronary occlusion and traumatic angina pectoris. He states that the best evidence of myocardial damage in traumatic chest cases is electrocardiographic changes soon or immediately after the injury.

Moritz and Atkins [12] produced myocardial contusions in 32 dogs by striking the exposed hearts with a uniform force. They noted that, pathologically, cardiac contusion is almost indistinguishable from non-traumatic myocardial infarction.

Kissane,[10] in his correlated studies of experimental cardiac injuries in 19 dogs, and of cardiac damage in 14 human beings, states that severe injury to the heart can take place in thoracic trauma without rib fracture. Electro-

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cardiographically, T, ST and other changes may not appear for 24 to 48 hours after the injury had taken place and they may be transient. Other electrocardiographic changes may remain from 12 to 18 months.

Leinoff [11] presents 10 cases with electrocardiographic evidence of heart damage resulting from non-penetrating chest trauma. All survived.

Anderson [1] states that cardiac damage from non-penetrating thoracic injuries may result in death from rupture of the heart or from ventricular fibrillation. Those who survive may recover completely or may remain with symptoms of angina pectoris or of cardiac insufficiency which may eventually lead to congestive failure and death. There may, however, be immediate survival from the original chest injury, with the presence of symptoms referable only to the contusion of the chest wall; then, a latent period of several days to months follows, and the concealed cardiac injury manifests itself as an aneurysm or results in congestive failure at a later date.

Barber [2] cites symptomless cases of non-penetrating chest injuries that recovered from the original mild contusions and later died of other causes, and traumatic cardiac lesions were demonstrated post mortem.

Thus, there is no doubt that many cases of myocardial contusion or damage to the heart in non-penetrating chest trauma are missed and not diagnosed. Since physical signs of cardiac contusion or of myocardial damage are often absent if the pericardium is not involved, the condition is not recognized unless repeated electrocardiographic tracings are made. The symptoms of pain, particularly on respiration, are usually ascribed to muscular contusion, or to "traumatic pleurisy." However, more definite symptoms of an anginal syndrome or of myocardial insufficiency may develop or become apparent later, after recovery from the initial chest trauma had taken place.

In order to avoid failure in diagnosis of cardiac damage in cases of chest trauma and in order to determine the frequency of such occurrence, it was decided to study all cases of non-penetrating chest injury admitted to this hospital. The study was made on ambulatory cases only. Every case, or as many as it was possible to investigate at a given time, admitted with a history of an injury to the chest, was carefully studied from the cardiac standpoint. In addition to a careful history and physical examination, at least one roentgenogram of the thoracic cage and a fluoroscopic examination were made. Repeated electrocardiographic tracings were made on subsequent visits in addition to the initial electrocardiogram on the first visit before a negative opinion as to cardiac damage was ventured.

Two different groups of cases were encountered and studied. One group consisted of seamen, longshoremen, Customs employees, WPA workers, and Post Office employees who sought medical aid because of an injury to the chest. The time interval between the accident and the first observation in this study varied in this group from several hours to as much as 10 weeks. The latter cases were usually those of seamen who had sustained the injury at sea, and who had not reached the home port until after a considerable length of time. Among these were individuals who had received first aid,

such as strapping of the chest aboard ship, and some who had also been examined and treated in hospitals in different countries where the ship had stopped during the trip. On the other hand, there were some who at first had not considered the chest injury sufficiently disabling to merit medical attention, but reported for treatment many weeks later, when symptoms persisted or had returned. The period of observation during this study varied in this group between four weeks and one year, or longer.

The second group encountered consisted of longshoremen and seamen, and Employees' Compensation beneficiaries. Most of these came under observation because they had complained of symptoms referable to the cardiovascular system which they either connected with or attributed to a previous chest injury. Many of these were admitted at the request of the U. S. Employees' Compensation Commission for purposes of diagnosis and opinion as to causal relationship between the previous trauma and the alleged subsequent disability. The lapse of time between the injury in this group and the first observation varied between three and 18 months or more. The period of observation in this group varied between one or two examinations for purposes of diagnosis, to a follow-up as long as a year or more.

In the first group, the initial examination was made on 286 patients. Of these, 72 failed to return for reëxamination at the proper time, or did not report at all, and so they were dropped from the list. Of the remaining 214, five were females and 209 were males. The age extremes varied between 18 and 76 years. In the second group, the first examination was made on 42 individuals, six of whom failed to return for follow-up or further observation. Of the remaining 36, all were males. The age extremes varied between 30 and 78 years.

In 168 cases of the 250 studied in both groups, chest trauma resulted from a fall from various heights, from that of the ground level or in a bath tub to that of two stories. In 38 instances, thoracic trauma resulted from a falling or swinging object striking the trunk. In 28, injury followed crushing of the chest between objects or a fall plus a blow from a falling or sliding weight. In 11 cases chest injury resulted from a fist fight and in eight cases from an automobile accident. In 84 per cent of the cases, the injuries occurred on the job. In four instances from both groups injury to the chest occurred on two different occasions during the period of observation.

The total number of fractured ribs in both groups was 321. There were two fractured scapulae among these. There was only one incident of first rib fracture and two cases of second rib fracture. Considering that this study was carried out on ambulatory patients only, one would a priori conclude that there were no seriously injured chest cases among them. Hence, the chances of cardiac injury among such patients should be slight. This assumption might be justified for the first group of 214 cases studied. Indeed among this group many had rather mild impacts with resulting injury to the chest wall and were discharged as recovered within a month or so. The chances of cardiac injury were, therefore, comparatively small as will be

TABLE I

Non-Penetrating Chest Injuries

| | Age in Decades | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group I | | | | | | | |
| | 10–20 | 21–30 | 31–40 | 41–50 | 51–60 | 61–70 | 71–80 | Totals |
| Number | 2 | 16 | 47 | 68 | 63 | 17 | 1 | 214 |
| Number with rib fractures | | 4 | 14 | 27 | 24 | 6 | | 75 |
| | Group II | | | | | | | |
| Number | | 1 | 6 | 7 | 11 | 9 | 2 | 36 |
| Number with rib fractures | | | 2 | 5 | 6 | 6 | 2 | 21 |
| Totals | 2 | 17 | 53 | 75 | 74 | 26 | 3 | 250 |

noted subsequently. The second group, however, consisted mostly of more seriously injured, many of whom had been hospitalized for a considerable period of time following the accident. Unfortunately, no serious cardiac study had been made during such period of hospitalization or soon after the accident in these cases, with the exception of three or four, and in only two instances were electrocardiographic tracings made prior to the beginning of this study. This testifies to the rarity of the occasion when an injured chest case might be considered to have also sustained a cardiac injury. It is little wonder then, that Bright and Beck [7] state that the vast majority of cases of cardiac damage in non-penetrating chest trauma are not recognized and not diagnosed.

TABLE II

Time Interval between the Accident and the First Examination in This Study

| | Group I—214 Cases | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 Hours to 1 Week | 1–2 Weeks | 2–3 Weeks | 3–4 Weeks | 4–6 Weeks | 6–10 Weeks | Total |
| Number of Cases | 93 | 53 | 27 | 13 | 18 | 10 | 214 |
| | Group II—36 Cases | | | | | | |
| | | 3 to 6 Months | | 7 to 12 Months | | 13 to 18+ Months | |
| Number of Cases | | 16 | | 15 | | 5 | 36 |

Among the first group there were encountered 26 cases of various cardiac abnormalities that were thought not to be related to or influenced by the chest injury. In most cases a history of such an existing condition was obtained. Thus, there were 10 cases of hypertension, eight of arteriosclerosis, including sclerotic aortic arch and coronary disease, four of rheumatic heart disease and four of cardiovascular syphilis including two cases of aneurysm of the aorta. Most of these were more or less non-symptomatic during the period of observation for the chest injury.

Among the first group of the relatively mild, non-penetrating chest injuries, 15 cases (about 7 per cent) of cardiac damage were encountered. These were thought to be either directly due to the injury or aggravated by the injury.

### Case Reports

*Case 1.* A colored, WPA laborer, aged 50, fell from a scaffold into a manhole, about 20 feet, and struck his chest. He was treated by a local physician for about a week and when he did not improve, he came here for physiotherapy. On examination 10 days after the injury, he claimed to have been having a dull ache over the precordium ever since the accident. He never had had it before. There were no external signs of injury. Heart sounds were good in quality; rate and rhythm were normal. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. There were fine râles in the right base; there was no evident dyspnea. Fluoroscopy of the heart and aorta was negative. Roentgenogram of the ribs was negative. Electrocardiogram was normal. Urine was normal and Wassermann reaction negative. On return for reexamination two weeks later he stated that he had not returned the week before because he had been worse and that he had been in bed since his last visit. At this time the findings were about the same except for more râles in the right base. Temperature was 37° C.

Electrocardiogram 10 days after the injury was negative except for left axis deviation and occasional extrasystole. Two weeks later $T_2$ was inverted and $T_4$ was inverted. This pattern continued on several succeeding tracings with a gradual return to normal. Fourteen weeks later $T_2$ and $T_4$ were upright. The cardiogram was considered normal.

*Diagnosis.* Myocardial damage following cardiac contusion, with recovery.

*Case 2.* A seaman, aged 42, slipped and fell on deck of the ship and struck the front of his chest. Ten days later he reached port and came to the hospital complaining of substernal and precordial pain on motion and on effort. He had never had any symptoms referable to the cardiovascular system prior to this injury.

On examination there were no external signs of injury. Heart sounds were normal, rate 90, regular sinus rhythm. Blood pressure was 106 mm. Hg systolic and 80 mm. diastolic. Temperature was 37° C. There were fine râles at the left base. Fluoroscopy showed a triangular looking heart, otherwise negative. Roentgenogram of the thorax was negative for fractures. Wassermann reaction was negative.

Electrocardiogram showed "M" type $QRS_2$, flat $T_3$, left axis deviation and shallow inversion of $T_4$. Four weeks later it showed improved voltage in Lead II, inverted $T_3$ with a well defined, upright $T_4$.

*Diagnosis.* Myocardial contusion, recovered.

*Case 3.* A WPA social worker, female, aged 47, was in an automobile accident and fractured her left arm and struck her chest. She was at a hospital for about 10 weeks, after which she came to this hospital for physiotherapy. She had no symptoms referable to the heart. On examination, the heart sounds were good in quality, rate and rhythm were normal. Blood pressure was 130 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy of the heart and aorta was negative. Roentgenogram showed healing fractures of the fifth to eleventh ribs inclusive, on the left side in the anterior and posterior axillary line.

Electrocardiogram 11 weeks after the accident showed an isoelectric $T_2$ and inversion of $T_3$ with low amplitude of $T_4$. Four weeks later it showed partial inversion of $T_4$, in addition to $T_2$ and $T_3$ changes. Repeated examination every month showed a gradual return of the electrocardiogram to normal. Twelve months after injury $T_1$ was normal, $T_2$ still of low amplitude, but $T_4$ was upright.

*Diagnosis.* Myocardial damage, posterior lesion, recovered.

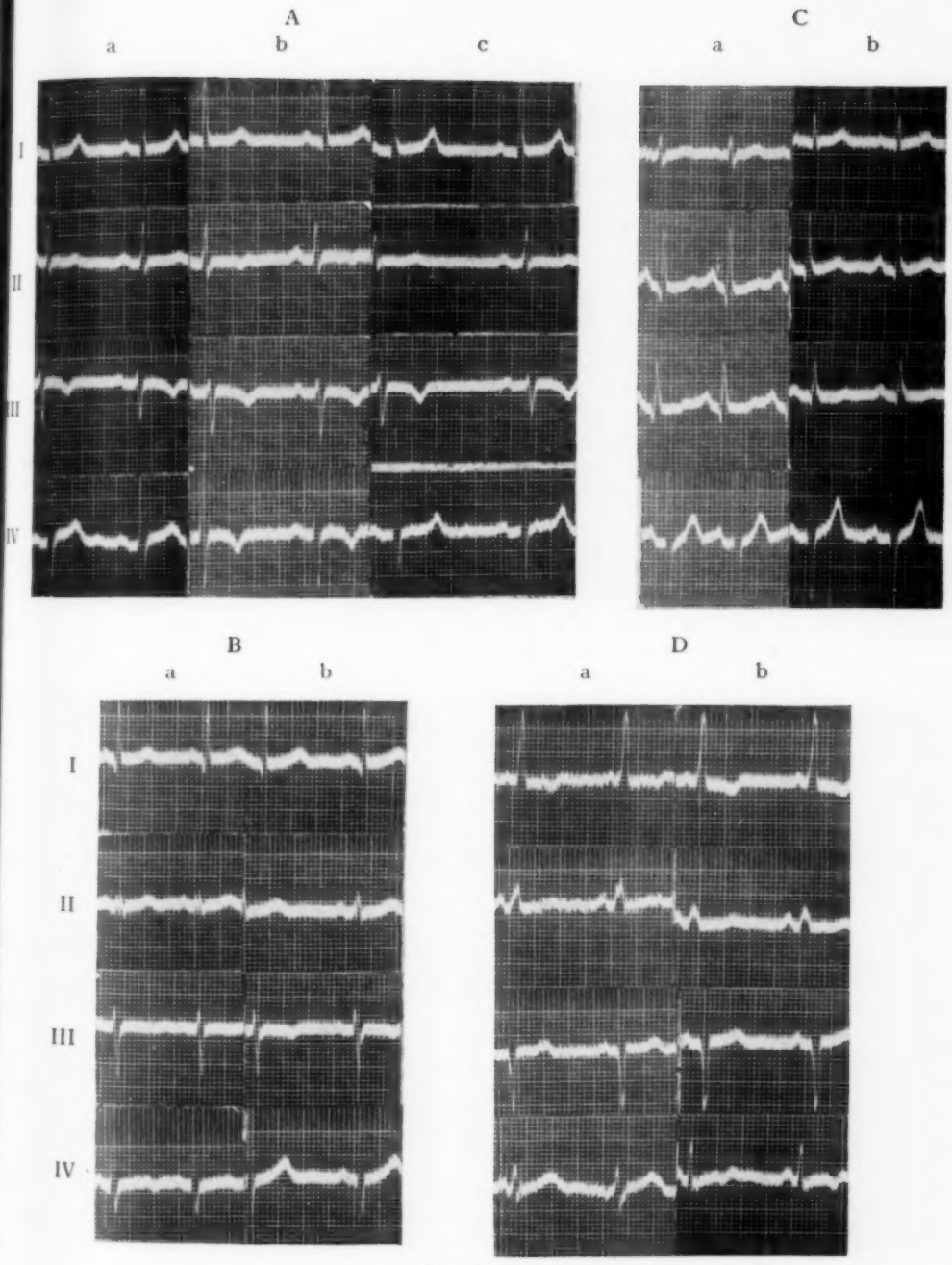


FIG. 1.

A. Case 1 (a) Taken 10 days after the injury.
(b) Two weeks later.
(c) Sixteen weeks after the accident.

B. Case 2 (a) Ten days after the accident.
(b) Four weeks later.

C. Case 4 (a) Two weeks after injury.
(b) Six weeks after injury.

D. Case 28 (a) Eleven months after the accident.
(b) Four months later.

*Case 4.* A Post Office employee, aged 58, fell from a height of five feet against a pile of lumber and struck his chest. He received first aid treatment and was able to resume his work. One week later he developed shortness of breath and precordial pain on effort which was thought to have been due to pleurisy resulting from the injury. On examination two weeks after the accident, the heart sounds were normal, rate 110, rhythm regular. Blood pressure was 106 mm. Hg systolic and 84 mm. diastolic. Temperature was 37° C. The bases of the lungs were clear. There was slight peripheral arteriosclerosis. Eye grounds and urine examination were negative. Fluoroscopy of the heart and aorta was negative. Roentgenogram showed fractures of the ninth to twelfth ribs inclusive, on the right side.

Electrocardiogram two weeks after injury revealed low voltage in Lead I, low amplitude of $T_2$; and the presence of $Q_2$, $Q_3$, and $Q_4$, the latter only 2 mm. deep, not characteristic. The patient was told to stay in bed for a month. Six weeks after the injury all T-waves were well defined, improved voltage in all leads, $Q_2$ and $Q_3$ much less pronounced, $Q_4$ absent. The patient returned six months later stating he had no symptoms and that he was able to resume his work. Electrocardiogram was negative.

*Diagnosis.* Myocardial contusion, recovered.

*Case 5.* A WPA painter, aged 58, fell off a scaffold from a height of nine feet and struck his chest against a plank. He had been in bed at home for two weeks after the injury and then came to this hospital for physiotherapy. On examination three weeks after the accident, he stated that he had never had precordial pain or dyspnea before, even on exertion, but for the past two weeks he had been having dyspnea on effort and pain over the sternum not radiating in any direction. The heart sounds were distant; rate and rhythm were normal; there were no murmurs. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. Roentgenogram showed slight pleural effusion on the left, with fracture of the seventh to eleventh ribs inclusive, on the left side. The heart and aorta were normal. Temperature 37° C.

Electrocardiogram showed isoelectric $T_3$ and almost absent R in the precordial lead with a low amplitude $T_4$. Two weeks later $T_1$ was low and diphasic, $T_2$ almost flat, $T_3$ isoelectric, but the precordial lead was normal. Seven weeks after injury rather low $T_1$, otherwise normal.

*Diagnosis.* Probable myocardial contusion with anginal syndrome.

*Case 6.* A sea captain, aged 51, slipped on a gangplank and struck the left side of his chest. He had pain, but not severe enough to keep him away from his duties as Master of the ship. He reached port 10 days after the injury. On examination he complained of precordial pain radiating to the left arm. He had never had such pain before. He was well nourished and robust without evident dyspnea. Temperature was 98° F. Heart sounds were good in quality. There was a blowing systolic murmur at the apex; rate and rhythm were normal. Blood pressure was 136 mm. Hg systolic and 90 mm. diastolic. The bases were clear. Roentgenogram showed no rib fracture. Fluoroscopy showed a normal looking heart and aorta. The blood Wassermann reaction was negative.

Electrocardiogram showed partial inversion of $T_4$ with a $Q_4$ of 3–4 mm. The limb leads were normal. Ten days later, and three weeks after the injury, the T in the precordial lead was diphasic, limb leads were the same as on the first examination. Five weeks after the injury the precordial lead was normal.

*Diagnosis.* Contusion of the chest and myocardium, recovered.

*Case 7.* A longshoreman, aged 49, fell from a gangplank for a distance of 13 feet, and struck his chest. After resting for a while, he attempted to resume work, but could not on account of pain in the chest. Three days later he was taken to a hospital with pneumonia. He recovered, but continued to feel short of breath on exertion, and had precordial pain not radiating in any direction. He had never had such symptoms before the injury. On examination five weeks after the accident, he

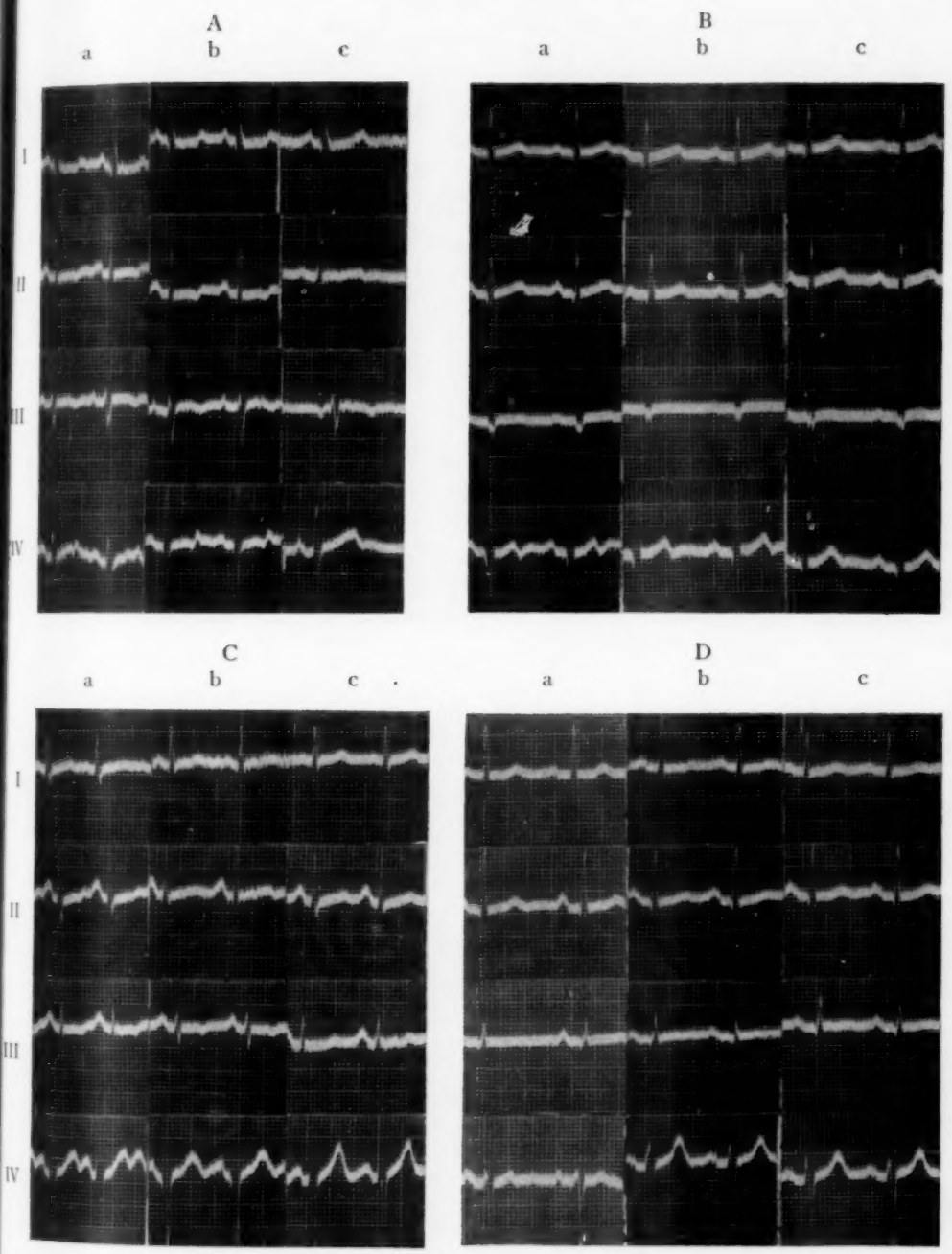


FIG. 2.

A. Case 3 (a) Eleven weeks after the injury.
(b) Fifteen weeks later.
(c) Twelve months after the accident.

B. Case 6 (a) Ten days after injury.
(b) Three weeks after injury.
(c) Five weeks later.

C. Case 7 (a) Five weeks after injury.
(b) One week later.
(c) Two months after injury.

D. Case 5 (a) Three weeks after injury.
(b) Two weeks later.
(c) Seven weeks after the accident.

appeared well nourished and had good color. The heart was not enlarged; sounds had a "tic tac" quality; rate was 110. The blood pressure was 124 mm. Hg systolic and 90 mm. diastolic. The bases of the lungs were clear. There was no edema; the liver was not enlarged. Fluoroscopy of the heart and aorta was negative. Roentgenogram showed fracture of the left seventh rib in the anterior axillary line. Electrocardiograms five weeks after the accident showed flat $T_1$, low $T_2$ and inverted $T_3$. One week later, $T_2$ was flat to partially inverted. Two weeks later, and eight weeks after the injury, the electrocardiogram returned to normal.

*Diagnosis.* Contusion of the chest and myocardium followed by pneumonia, with recovery.

The foregoing case reports had in common the absence of symptoms prior to the accident, the absence of physical signs such as cardiac enlargement, valvular lesions, or hypertension, which would indicate previous cardiac abnormality. In nearly all cases recovery was the rule, symptomatically as well as cardiographically. The following cases denote to a greater or lesser extent the evidence of some cardiac abnormality such as hypertension, coronary sclerosis or a rheumatic infection with cardiac enlargement, which must have antedated the injury. However, it is believed that the injury either aggravated a preëxisting condition or caused superimposed damage.

*Case 8.* A ship's carpenter, aged 61, fell on the deck of the ship and struck his chest. He was treated by a local doctor for about six weeks and was told to return to duty. There was no record that this man had any cardiac study during this interval. On examination eight weeks after the injury, he complained of shortness of breath and pain in the chest on exertion. He had never had such symptoms before. Heart sounds were normal. There were no murmurs. The aortic second sound was accentuated. Blood pressure was 142 mm. Hg systolic and 90 mm. diastolic. There were râles and a friction rub in the left subaxillary space. Fluoroscopy revealed slight cardiac enlargement to the left and the aortic arch was slightly widened. Roentgenogram showed fracture of the sixth to eighth ribs inclusive, on the left side. Urine was negative. Wassermann reaction was negative. Electrocardiograms eight weeks after injury revealed $T_1$ almost isoelectric, $T_2$ and $T_3$ inverted, $T_4$ bifid, slight left axis deviation. Six weeks later $T_1$ was well defined, $T_2$ low but upright, left axis deviation.

Two months later he had improved symptomatically, the pain had disappeared, but he still had shortness of breath on exertion. The electrocardiogram showed a return to normal. The blood pressure was 170 mm. Hg systolic and 102 mm. diastolic, and there was definite cardiac enlargement, indicating a preëxisting hypertensive condition. Nine months after the injury he was still unable to return to his former, rather strenuous occupation, but he was able to work at light duty. The electrocardiogram showed only slight left axis deviation.

*Diagnosis.* Hypertension with myocardial contusion, probably related to the chest trauma.

The medicolegal aspect of this case was settled in favor of the claimant.

*Case 9.* A longshoreman, aged 44, was struck over the front of the chest by a steel beam of about 100 pounds in weight. On examination one day after the accident, he complained of substernal pain and "difficulty in breathing," with attacks of palpitation. He denied previous symptoms except occasional cough. The heart sounds were normal, rate 80, regular rhythm. Blood pressure was 120 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy was negative. Roentgenogram revealed

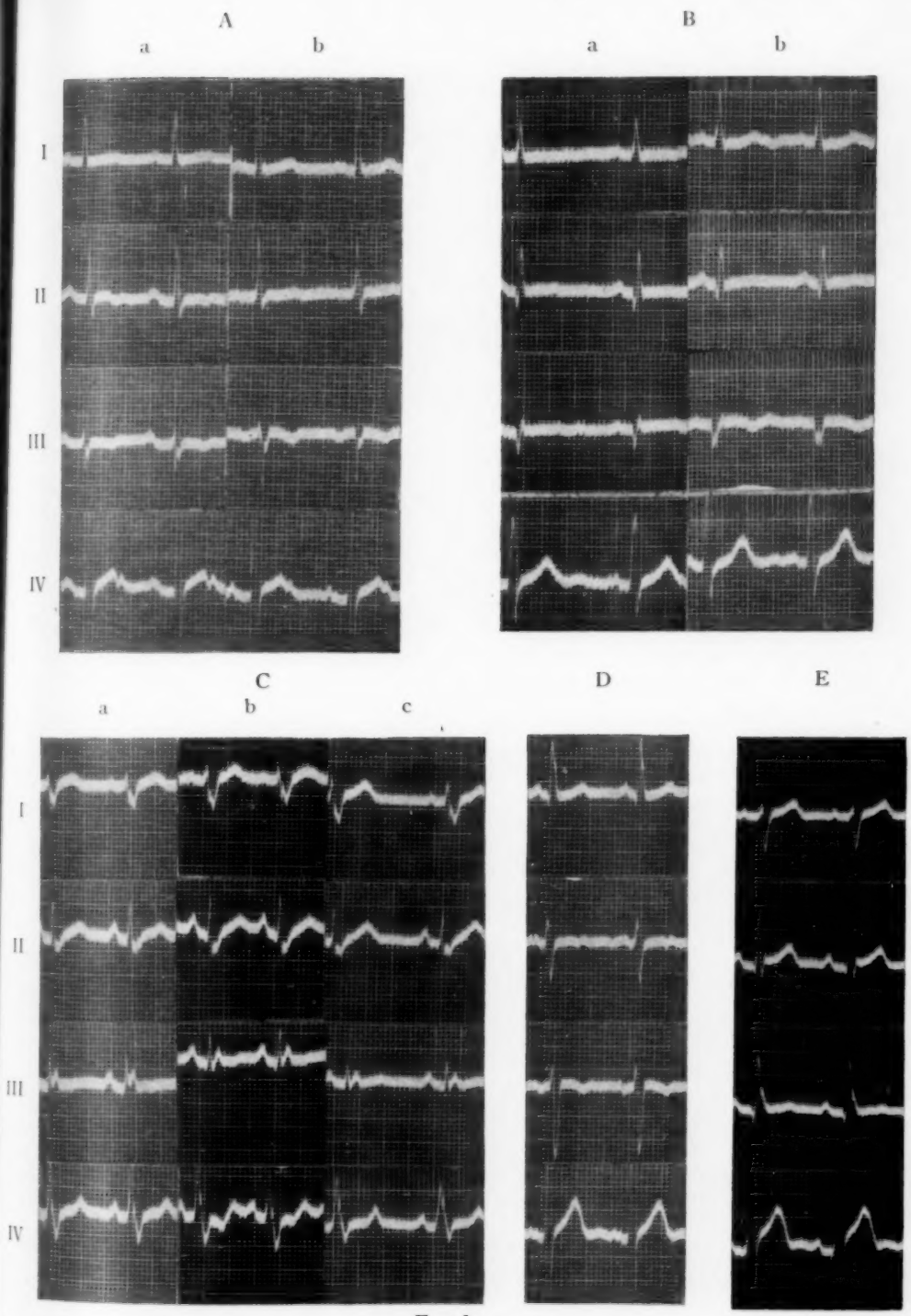


FIG. 3.

A. Case 8 (a) Eight weeks after the injury
(b) Six weeks later
B. Case 11 (a) Seven weeks after the injury
(b) Six weeks later
C. Case 16 (a) Four months after injury
(b) Three weeks later
(c) Nine months later
D. Case 19 Six months after injury
E. Case 21 Five months after injury

no fractured ribs. The electrocardiogram showed right axis deviation on repeated examinations. He had persistent anginal attacks with occasional "rapid heart action."

*Diagnosis.* Anginal syndrome with possible paroxysmal tachycardia, and slight emphysema. It is believed to be causally related to the injury.

*Case 10.* A 54 year old seaman fell out of his bed and struck the back of his chest. On examination two days later he complained of pain below the right scapula. He also developed a cough and brought up blood-tinged sputum after the injury. The temperature was 98° F. Heart sounds were normal, rate 110, regular sinus rhythm. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. There were râles in both bases of the lungs. Fluoroscopy showed a high left diaphragm with slight mediastinal shift to the left and increased density at the left base. Roentgenogram of the ribs was negative. Electrocardiogram two days after the injury showed marked left axis deviation, low $T_1$ and slurred QRS complexes. He continued to get anginal attacks for several months but he gradually improved. The electrocardiogram showed no change.

*Diagnosis.* Coronary sclerosis, old, with anginal syndrome which was probably aggravated by the chest trauma.

*Case 11.* A Post Office laborer, 62 years of age, was struck over the left side of the chest by a sliding, heavy, wooden box. He was able to continue to work, but three days later he began to have precordial pain on exertion. There was a history of hypertension without symptoms. On examination six days after the injury took place, he was tender over the left axillary region. There was a long, blowing systolic murmur over the apex, no thrill, rhythm was normal, rate 76. Blood pressure was 156 mm. Hg systolic and 88 mm. diastolic. Bases of the lungs were free. There was no edema of the extremities. There was slight peripheral arteriosclerosis, and slight changes in caliber of the retinal arteries. Fluoroscopy showed moderate to marked cardiac enlargement to the left and right, with prominence of the aortic arch. Roentgenogram was negative for fractures of the ribs. The urine showed a faint trace of albumin. Electrocardiogram seven days after the injury showed isoelectric $T_1$, almost flat $T_2$ and $T_3$, with $Q_2$ and $Q_3$. Six weeks later $T_1$ became upright and $T_3$ inverted. All QRS complexes were slightly slurred.

*Diagnosis.* Hypertensive heart disease with myocardial damage, the latter probably precipitated or aggravated by the chest trauma.

*Case 12.* A longshoreman, aged 54, was thrown against the side of a ship when he was struck by a swinging draft of castor beans of almost 500 pounds weight. He was taken to the hospital by ambulance, had his chest roentgen-rayed, and was sent home. He was treated by a local physician for about six weeks. No study was made of his heart. On examination 10 weeks after the accident he denied ever having had cardiac symptoms before. He stated that two days after the injury he had developed shortness of breath, palpitation and pain in the chest. He spat up bloody sputum for several days. He had not been able to return to work because of dyspnea on effort. The heart was enlarged to the left. Sounds were distant, rhythm irregular, rate 100. There was a blowing systolic murmur at the apex and a distant, late, diastolic murmur at the same area. Blood pressure was 118 mm. Hg systolic and 84 mm. diastolic. There were no râles in the lungs. There was no edema; the liver was not tender. Eye grounds were not remarkable. Fluoroscopy showed marked enlargement of the heart to the right and left with obliteration of the retrocardiac space by an enlarged left auricle. Roentgenogram of the ribs was negative. Wassermann reaction and urine were negative. Electrocardiogram showed auricular fibrillation, rate 100, with no axis deviation.

*Diagnosis.* Probably rheumatic heart disease with failure precipitated by trauma.

In this case the possibility of a ruptured mitral valve or damaged papillary muscle could be considered as a diagnosis. However, the marked cardiac

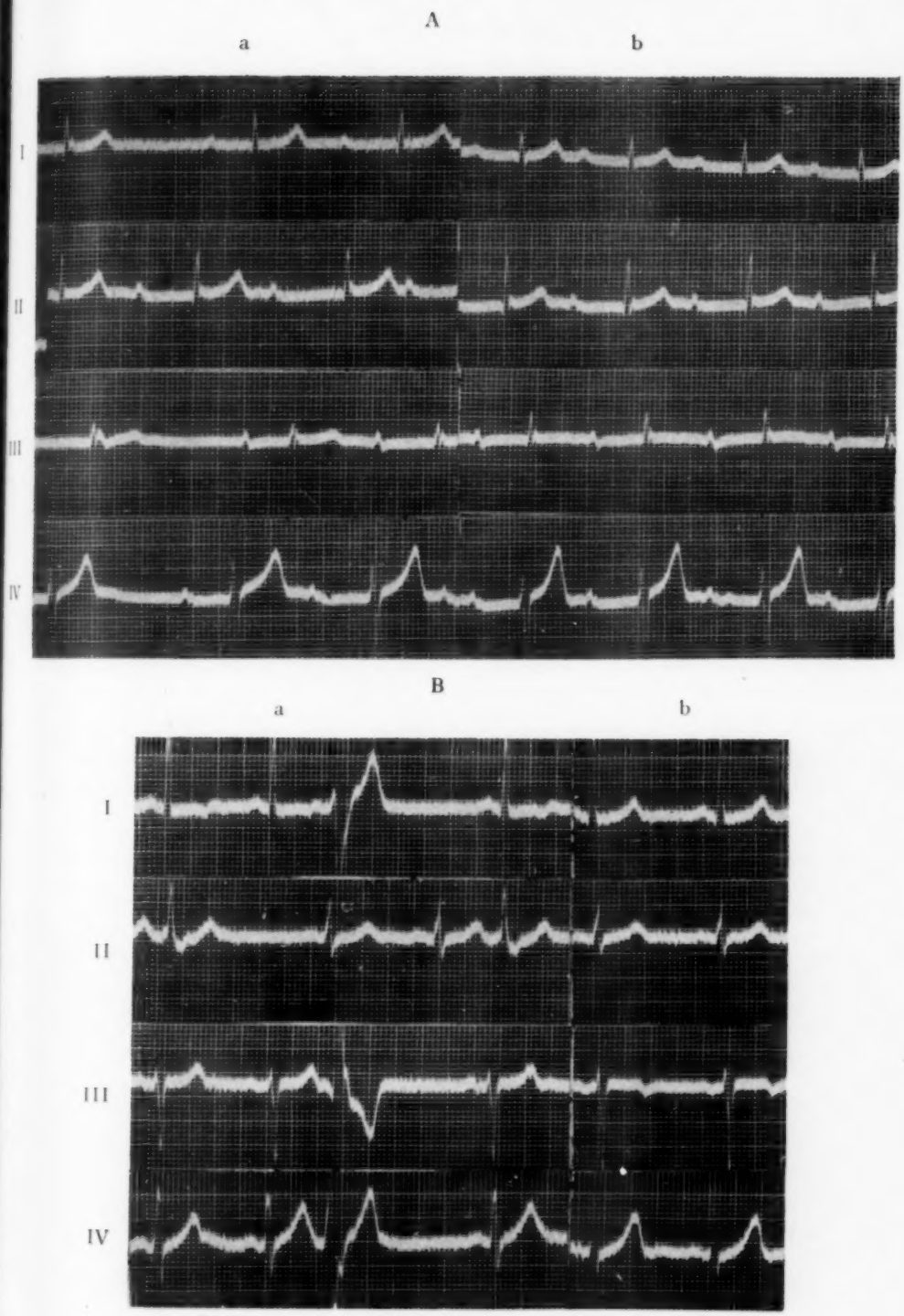


FIG. 4.

A. Case 17 (a) Twenty months after the accident
(b) Two weeks later

B. Case 18 (a) Six months after the injury
(b) Three months later

enlargement noted 10 weeks after the accident was more easily explained by a probable previous rheumatic endocarditis, even though the history was of no help in this respect. Medicolegally, the disposition of this case was in favor of the claimant.

*Case 13.* A longshoreman, 31 years of age, fell from a height of 10 feet and struck his chest against a cement floor. He did not lose time from work, but noticed "palpitation and fluttering" since the accident. On examination six weeks after the injury, the heart was not enlarged, sounds were normal, rate 74, with frequent premature beats. Blood pressure was 108 mm. Hg systolic and 80 mm. diastolic. Fluoroscopy was negative. Roentgenogram of the thorax was negative for fractures. The electrocardiogram showed numerous ventricular extrasystoles. The latter continued subjectively for about two months and subsided.

*Diagnosis.* Extrasystolic arrhythmia, probably precipitated by chest trauma.

Since no time from work was lost in this case, compensation was not awarded.

*Case 14.* A customs guard, 50 years of age, slipped from a staircase and fell against a rail, striking the front of his chest. One week later he began to have pain in the chest which did not radiate in any direction. The pain was not accompanied by dyspnea; it was worse on exertion, and was relieved by rest. On examination three weeks after the injury, the findings were entirely negative. Blood pressure was 118 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy was negative, and roentgenogram of the thorax revealed no fractures.

Electrocardiogram showed low $QRS_2$ of the "W" type with a deep $Q_3$, 9 mm., and $S_1$. The cardiogram did not change on subsequent examinations whereas the symptoms varied from time to time.

*Diagnosis.* Coronary disease, old, with anginal syndrome, possibly aggravated by the injury.

*Case 15.* A longshoreman of 50 fell from a height of about 10 feet and struck his chest, elbow and leg. He attempted to continue to work, but was forced to give up on account of pains. He was examined six days after the injury by the carrier's physician and was sent to the hospital where he had remained for 11 days, after which he had been given out-patient treatment for about six weeks. No cardiac study was made at that hospital.

On examination about 10 weeks after the accident he stated that he had been short of breath on slight exertion, accompanied by precordial pain. He had never had such pain before, and never had been short of breath.

He was obese and was somewhat dyspneic during the examination. Color was fair. Heart sounds were normal, rate 100, regular rhythm. Blood pressure was 160 mm. Hg systolic and 116 mm. diastolic. There was no edema and there were no râles in the bases. There were no remarkable changes in the eye grounds. Fluoroscopy showed slight left ventricular enlargement, but roentgenogram of the heart was negative. The left side showed healing fractures of the seventh to ninth ribs inclusive at the anterior axillary line. Urine revealed a slight trace of albumin. Electrocardiogram showed slurring of all QRS complexes, with deep $Q_3$ and inversion of $T_3$ on three different occasions.

*Diagnosis.* Coronary disease with anginal syndrome, the latter probably precipitated by the thoracic injury.

The U. S. Employees' Compensation Commission allowed partial claim in this case.

In addition to the above cases there were two others in which, subsequent to the injury, paroxysmal tachycardia appeared on occasions although it was said never to have existed before. Because no electrocardiographic record was ever made of the tachycardia attack, the case records are not reported and not included in the list.

Among the 36 individuals studied in the second group, there were two cases of chronic nephritis, two of cardiovascular syphilis and three of hypertension, who were not considered disabled. These conditions were not influenced by the injury in question. Thirteen out of 36 were found to have been suffering from conditions which were thought to be either caused or aggravated by the accident.

Among these cases there was a more definite and persistent attempt on the part of the patient to ascribe all the symptoms to the injury. Whereas in the previous group, in most instances the individual complaining of symptoms referred to the chest, in this group many of them definitely pointed to the heart and were "heart conscious." In many instances this attitude was the result of attempts at medicolegal action or of measures preparatory to such claims because of the accident.

### Case Reports of Group II

*Case 16.* A seaman, aged 46, fell off a ladder and struck his chest, then dropped 10 feet lower and struck his left side against a rail. He received first aid treatment aboard ship and roentgenographic examinations and treatment at several ports in Europe and Asia during his trip. He was told "two ribs were broken on the left side near the heart." He worked only part of the way. He came to this hospital four months after the accident when he reached home port. On examination he complained of shortness of breath on exertion accompanied by pain around the heart. This began about two months following the accident. He had never had such symptoms before. There was, however, a questionable history of pulmonary tuberculosis. The heart was not enlarged; sounds were good in quality; rate and rhythm were normal. Blood pressure was 100 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy was negative. Roentgenogram showed no fractures of the ribs, but revealed evidence of healed apical tuberculosis. The blood Wassermann reaction was negative. Urine was negative.

Electrocardiogram four months after the accident showed intraventricular block. Three weeks later there was no change except for a depression in the $ST_4$ segment. Nine months later there was still evidence of intraventricular block, but with the precordial lead nearing the normal.

*Diagnosis.* Intraventricular block, permanent, probably resulting from myocardial contusion.

*Case 17.* A machinist of 42 was violently blown out of a boiler which he had been repairing aboard a ship, by a sudden blast of compressed air and steam. He was thrown for a distance of 12 feet against an iron grating and he received a severe blow on the left side of the chest. He was hospitalized for several months. At the hospital it was discovered within about a month after admission that he had "heart block." He was treated as an out-patient for another year or so.

On examination a little over 18 months after the accident, he claimed that he had been suffering from shortness of breath on exertion and that he had not been able to return to work because of that. He had no rheumatic or syphilitic history. He stated that prior to the accident he had never lost a day from work because of illness.

His work was rather strenuous. There were no external abnormalities. Heart sounds were of good quality at times and muffled at other times. The rate was 44 and the rhythm irregular. Blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. Fluoroscopy revealed a normal looking heart and aorta with slow and irregular action. Roentgenogram of the thorax was negative for fractures. Blood Wassermann reaction and urine were negative.

Electrocardiogram 20 months after injury showed auriculo-ventricular block, with an auricular rate of 56 and a ventricular rate of 46. Both were irregular. There were no other changes. There was no change after exercise. Two weeks later rhythm was regular, the auricular rate 66 and the ventricular rate 66. The PR interval was .44 second. After exercise, it returned to the identical rate with dissociation as in the previous tracing.

*Diagnosis.* Complete heart block, permanent, following chest trauma.

The medicolegal aspect was decided in favor of the claimant and full compensation was granted by the U. S. Employees' Compensation Commission.

*Case 18.* A longshoreman, 61 years of age, fell down into the hold of a ship for about 16 feet. He was unconscious and was taken to a hospital where he remained for 11 days. Subsequently he was treated with physiotherapy for about five months, as an out-patient, by the carrier's physician. The hospital record revealed "the presence of auricular fibrillation with partial heart block, rate 42, due to old coronary disease." No electrocardiogram nor roentgenogram of the heart was made. On examination six months after the accident he complained of shortness of breath and of occasional precordial pain. He stated that he had never had such symptoms before, and that he had never lost time on account of heart ailments, even though he had been doing strenuous work. He showed no dyspnea during examination. The heart sounds were distant. There were no murmurs. There was a trigeminal rhythm. Blood pressure was 140 mm. Hg systolic and 92 mm. diastolic. There were no râles in the bases; and there was no edema. There was moderate peripheral arteriosclerosis and slight narrowing of the retinal arteries. Urine showed a faint trace of albumin, no casts. The Wassermann reaction was negative. Fluoroscopy showed no cardiac enlargement and the aorta was normal. Roentgenogram showed a healed fracture of the fifth rib on the right side at the midclavicular line.

The electrocardiogram showed a ventricular, premature contraction every third beat with inversion of $T_1$ after every normal beat, and left axis deviation with slurring of all QRS complexes. There was no history of digitalis medication. Three months later the trigeminal rhythm disappeared, and $T_1$ became upright. There was left axis deviation and slight slurring of QRS complexes.

*Diagnosis.* Myocardial damage with anginal syndrome following chest trauma; old coronary disease.

Partial compensation was granted by court.

*Case 19.* A seaman, aged 42, fell down in the engine room from a height of about five feet to the floor. He struck his elbow and chest. He was hospitalized on account of an infection that developed at the site of the injury of the elbow. During his stay at the hospital he had no cardiac symptoms and no study of the heart was made. On examination six months after the injury, he stated that he had been having precordial pain and a "jumpy feeling in his heart" for about three months; that is, it began about three months after the accident. He had never had such symptoms before. There were no external signs of injury. Color was good. No dyspnea was noted. Heart sounds were good in quality; rate and rhythm were normal; blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. Fluoroscopy was negative.

Roentgenogram showed fractured left fifth and sixth ribs in two places, healed. Blood Wassermann reaction was negative. Electrocardiogram showed slurred QRS, marked left axis deviation, partial inversion of $T_2$ of low amplitude, and inversion of $T_3$.

*Diagnosis.* Anginal syndrome with coronary disease, probably precipitated or aggravated by the chest injury.

*Case 20.* A longshoreman, 37 years of age, fell from a height of 10 feet and struck his chest. He was taken to the hospital, and there he developed "pneumococcal pleurisy." He was discharged three weeks later and was treated for several months by a local physician for his fractured ribs. There was no record of any cardiac study. On examination five months after the accident, he stated that he had been having pain in the left side of the chest on effort, ever since the injury or soon after that; rest relieved the condition. He had never had such symptoms before. The past history was not significant. Findings were entirely negative, aside from a blood pressure of 80 mm. Hg systolic and 64 mm. diastolic. There was dyspnea at rest. Fluoroscopy was negative. Blood Wassermann reaction and urine were negative. Roentgenogram showed healed fractures of the fifth to the ninth ribs, inclusive, on the left side.

Electrocardiogram showed slight slurring of all QRS complexes with slightly widened $S_1$ and $S_2$, but with the QRS interval within normal limits.

*Diagnosis.* Coronary disease with angina pectoris; the anginal syndrome was probably initiated by the chest trauma.

Compensation was granted in this case until symptoms subsided.

*Case 21.* A seaman, aged 40, jumped out of a second story window while intoxicated. He was hospitalized for three months and was discharged as recovered. The hospital diagnosis was "multiple fractures of the first to seventh ribs, inclusive, on the right side; of the mandible and of the greater trochanter on the right side." Roentgenogram reported a "mitral configuration of the heart, but there was no enlargement. Clinically, the heart was negative." No electrocardiogram was made. On examination here, five months after the accident, he complained of precordial pain of two weeks' duration, with dyspnea on exertion. He denied syphilitic or rheumatic infection. The heart was enlarged to the right and left. There was a questionable gallop rhythm at the apex, rate 110. No murmurs were heard. There was no palpable thrill. Blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. Bases were clear. There was no edema nor tender liver. Temperature was 37° C. Urine was negative. Wassermann reaction was negative. Fluoroscopy showed symmetrical enlargement of the heart on both sides, with a straight left border. Roentgenogram showed healed fractures of the upper seven ribs on the right side.

Electrocardiogram showed right axis deviation, slight $ST_2$ and $ST_4$ elevation, with slurring of QRS complexes.

The patient did not return for another examination until nine months later. At that time, the electrocardiogram had not changed and the symptoms occurred less frequently. The physical signs did not change.

*Diagnosis.* Myocardial damage following injury, probably superimposed upon a previous, quiescent, rheumatic heart disease.

The following cases demonstrate by the history, by the evidence of cardiac enlargement, as well as by the blood pressure, that preëxisting cardiac disease was present, but that the previously existing condition was not disabling, and did not prevent the individual from following up his occupation prior to the accident; that is, the preëxisting condition was quiescent or asymptomatic, but a break occurred or was initiated as a result of the injury or coincidental with the injury.

*Case 22.* A colored winchman, 63 years of age, fell on the deck and struck his chest when he was hit by the flap of a heavy canvas tent, against which a gust of wind suddenly blew. He received first aid and continued to work for several days. He had to give up work, however, as he began to feel short of breath. He was treated by a local physician for two months and when he became worse, he was hospitalized.

On examination seven months after the injury, he complained of shortness of breath and pain in the chest not relieved by rest, but aggravated on effort. He had two periods of hospitalization, one of 11 days, the other of 20 days. The hospital diagnosis was hypertensive and arteriosclerotic heart disease with decompensation. He claims never to have lost time because of sickness before. He used to have attacks of hiccups, and following the accident these had become worse and more frequent, so that an attack of singultus might last several weeks. It was in such a state that he had been admitted to the hospital on the second occasion.

At the time of examination at this hospital he appeared dyspneic. The heart was enlarged to the left; sounds were normal. There was a distant systolic murmur at the apex, rate 80, rhythm regular. The lungs were clear. There was slight edema of the ankles. The blood pressure was 200 mm. Hg systolic and 104 mm. diastolic. There was moderate peripheral arteriosclerosis and tortuosity of the retinal vessels. Urine showed a trace of albumin, but was otherwise negative. Wassermann reaction was negative. Fluoroscopy revealed slight dilatation of the ascending portion of the aorta and marked enlargement of the left ventricle. Roentgenogram showed no fractures of the ribs. He had had no digitalis for several weeks. Electrocardiogram showed high voltage, horizontal $RT_1$ and $RT_4$ depression, with marked axis deviation.

*Diagnosis.* Hypertensive and arteriosclerotic heart disease with mild congestive failure, probably precipitated by the chest trauma.

Partial compensation was awarded by the U. S. Employees' Compensation Commission.

*Case 23.* A longshoreman, aged 46, fell about 15 feet from a ladder to the boiler room. He fractured his right femur and hurt his chest. He had to undergo an operation for osteomyelitis of the femur as a result of the injury from which he apparently improved. Two years later, however, his heart became "bad," and he was told at a hospital that his heart condition had resulted from the injury of the chest.

On examination about 24 months after the injury, he appeared to be in a moderate degree of congestive heart failure. He showed pallor, dyspnea, orthopnea, râles in the bases, and peripheral edema. The heart was enlarged to the left; sounds were distant; rhythm was regular; and there were no murmurs. Blood pressure was 160 mm. Hg systolic and 128 mm. diastolic. He had had no digitalis. Urine showed a trace of albumin and a few hyaline casts. Fluoroscopy revealed moderate concentric hypertrophy of the heart in all directions. The aorta was full. Roentgenogram showed healed fractures of the right second rib and of the right scapula.

Electrocardiogram showed inversion of $T_1$ and $T_2$, diphasic $T_4$, and notching and slurring of QRS complexes, with an interval of .11 second.

*Diagnosis.* Hypertensive heart disease with myocardial damage and congestive heart failure, possibly related to a previous myocardial contusion.

Medicolegally this case was still pending and partial compensation was allowed.

*Case 24.* A longshoreman, 53 years of age, fell to the lower hold of the ship, about 28 feet, and broke "the cartilagenous sixth to eighth ribs" on the left side. Several hours after the accident, he developed dyspnea, orthopnea and cyanosis, with

auricular fibrillation. He was hospitalized and treated subsequently for about a year. On examination one year after the injury, he stated that he had been short of breath on the least exertion and had been taking digitalis ever since the accident. Before the injury he never was ill and was a hard worker, climbing four to five flights of stairs in his work, without symptoms. He had no rheumatic fever history and no syphilis. The heart was enlarged to the left; sounds were of good quality. There was a systolic murmur at the apex; rate was 110, irregular. Blood pressure varied between 160 mm. Hg systolic and 90 mm. diastolic and 200 mm. systolic and 104 mm. diastolic. The bases were clear. The liver was not tender. There was no edema. Color was good. There was no evident dyspnea at rest. Wassermann reaction was negative. Urine showed 4 plus albumin and hyaline and finely granular casts. The eyegrounds revealed changes in caliber of the arteries, no hemorrhages. Fluoroscopy showed moderate enlargement of the left ventricle. The aorta was normal. Roentgenogram of the chest showed no fractures.

Electrocardiogram revealed auricular fibrillation with digitalis T-waves, and right axis deviation. Several repeated cardiograms showed no changes.

*Diagnosis.* Hypertensive heart disease with auricular fibrillation and questionable old rheumatic mitral disease. Congestive failure was probably precipitated by the thoracic trauma.

This case was decided in favor of the claimant.

*Case 25.* A WPA architect, aged 64, fell on a level ground, struck his chest and fractured his left shoulder and humerus. He was never able to return to work because of shortness of breath which began after the accident. Recently the dyspnea had become much worse. He had had occasional "smothering sensation in the chest" for 10 months before the injury. On examination 11 months after the accident, he appeared obese and was slightly dyspneic. Heart sounds were good in quality; rate and rhythm normal. There was a fairly loud systolic murmur at the apex and base. Blood pressure was 150 mm. Hg systolic and 90 mm. diastolic; 170 mm. Hg systolic and 94 mm. diastolic. There were scattered râles in both bases. There was no edema. Fluoroscopy showed marked enlargement and triangular appearance of the heart, with prominence of the aortic arch. There were no rib fractures. Urine was negative.

Electrocardiogram showed a normal sinus rhythm, left axis deviation and $T_1$ inversion. There was moderate slurring of all QRS complexes and a low $T_2$. Four weeks later the T in the precordial lead became partially inverted and of low amplitude. No digitalis.

*Diagnosis.* Hypertensive heart disease with coronary disease, and myocardial damage probably aggravated by the injury.

*Case 26.* A longshoreman, aged 60, was struck over the chest by a bag of coffee weighing about 100 pounds. After resting for a while, he resumed work. The next day he was not able to work because of pain in the front and back of the chest. Two weeks later he developed shortness of breath which had become progressively worse. Since then he had not been able to return to work. He had never lost time from sickness before.

On examination about six months after the injury, he did not appear in distress, and his color was good. Heart sounds were masked by a long, blowing systolic murmur that was heard all over the chest. There was no thrill. Rhythm was regular, rate 100. There were no râles in the lungs and no edema. Blood pressure was 170 mm. Hg systolic and 96 mm. diastolic. He had had no digitalis. Urine was negative. Roentgenogram was negative for rib fractures. Fluoroscopy showed moderate enlargement of the left ventricle. The aortic arch appeared normal.

Electrocardiogram showed rather high voltage, slurring of all QRS complexes, and marked left axis deviation.

*Diagnosis.* Hypertension with coronary disease and anginal syndrome, probably initiated by the chest injury. The possibility of an injury to the mitral valve or papillary muscle was considered.

The following case reports illustrate more or less of a quiescent period or of only mild symptoms following the injury to the chest, terminating in one case in acute coronary occlusion and subsequent anginal attacks, and in the other in progressive anginal attacks and diminished cardiac reserve.

*Case 27.* A WPA carpenter fell off a scaffold, dropped about 15 feet, and struck his chest. He was treated for several weeks and was able to return to work. He continued to have occasional dull pain in his chest and shortness of breath on climbing stairs. One day, while at work, five months after the accident, he was seized with severe precordial pain and was taken to the hospital. The hospital record gave the diagnosis as "acute anterior myocardial infarction following a coronary occlusion." He recovered, but has not been able to return to work on account of frequent attacks of pain. He was examined here on three different occasions from eight to 12 months following the accident and three to five months following the coronary occlusion episode. The findings on all occasions were entirely negative, objectively. Blood pressure was 144 mm. Hg systolic and 90 mm. diastolic. Fluoroscopy was negative, and roentgenogram showed no evidence of fractured ribs. Wassermann reaction was negative. The electrocardiogram revealed slightly low voltage in all leads on all tracings.

*Diagnosis.* Myocardial contusion followed by coronary thrombosis and later by an anginal syndrome.

*Case 28.* A longshoreman, aged 59, fell off a hatch cover and struck his chest against a mooring winch. He was given first aid, had his chest strapped, and was allowed to continue his work. Several days later he began to feel pain and shortness of breath, so that he was not able to continue his work. He began to feel worse as time went on until he was having symptoms even at rest. On examination four months after the accident, he denied ever having had such symptoms before. He had had no rheumatic fever or syphilis. He appeared robust, and not in distress. There was slight carotid throbbing, but no distention of the veins in the neck. Heart sounds were distant and irregular, rate 104. No murmurs were heard. Blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. There were no râles in the lungs, no edema, nor tender liver. The thyroid was negative. Slight changes in caliber in the retinal arteries were present. Roentgenogram showed healed fractures of the ninth and tenth ribs on the right side. The left ventricle was enlarged two plus, with no auricular enlargement.

Electrocardiogram showed auricular fibrillation, rate 100, no shift in the electrical axis.

*Diagnosis.* Auricular fibrillation with angina pectoris, probably followed chest trauma.

Temporary compensation was allowed by the U. S. Employees' Compensation Commission.

## Discussion

As it appears from the case reports, nearly all the cases of cardiac damage in both groups were at the age when coronary disease and hypertension are most prevalent. Of the 28 cases, only three were in the early fourth decade. Table 1 shows that 60 per cent of all the individuals studied were in the fifth

and sixth decades of their lives, and 75 per cent of all the positive cases were in the same age group. This disproportion is presumably due to the fact that a large number of individuals in this age group was not entirely symptomless prior to the injury. It is well known, however, that a previously diseased heart is more vulnerable to trauma than a normal heart, and that greater damage is likely to result from injury to a heart or myocardium previously diseased, than from trauma to a normal heart under similar circumstances.

It is notable that the severity of the chest trauma and the chances of cardiac damage do not necessarily correspond. There were many cases of severe chest injury with bilateral rib fracture of as many as 11 and 13 ribs without cardiac involvement. In one instance an individual 56 years of age with a huge syphilitic aneurysm of the arch of the aorta sustained a moderately severe chest injury with fractured ribs, when his ship was torpedoed and he was exposed in a lifeboat for 48 hours. He showed no cardiac damage and was able to return to duty in less than three months. On the other hand, several cases of severe cardiac contusion with resulting permanent conduction defect were met with in individuals in whom no rib fracture or injury to the sternum was discovered. It is apparently the degree of elasticity of the chest wall and the type of blow which determine the chances of cardiac injury by anteroposterior compression. It is also conceivable that in cases in which fracture of ribs does occur, the force of the impact or blow is broken or diminished, thereby causing less or no damage to the substratum. In general, the greater the elasticity of the chest wall, the more chance for injury to the structures beneath, provided the impact is the same. In the cases reported here, the greater degree of cardiac damage occurred mostly among those who had sustained no rib fracture. In cases in which cardiac injury was considered to have taken place and in which fractured ribs were found, the latter occurred in a proportion of four on the right side to six on the left side of the chest.

The outstanding thing noted is that so few cases with relatively severe chest trauma had had a complete cardiac examination in instances in which the individuals were under treatment by the carrier's physicians. Nearly all those received physiotherapy for a relatively long time. Apparently it is still believed that the chest wall is a sufficiently strong barrier to internal injury in non-penetrating wounds, and that cardiac damage is the greatest rarity in such instances. Very possibly, many cases of cardiac disability allegedly resulting from trauma would have been eliminated from this number if a careful cardiac examination including a roentgenogram and an electrocardiogram had been made immediately after the accident. Since recovery is the rule in these cases, it is conceivable that if the cardiac injury had been discovered and the individuals treated accordingly, many cases might not have gone into the chronic stage or even have died eventually from the direct or indirect effects of the injury. It would also obviate and simplify many medicolegal problems, perhaps to the mutual advantage of plaintiff and defendant.

It is admitted, however, that in many instances it is very difficult to decide whether or not the cardiac disability is related to the trauma. It is to be borne in mind that many patients are apt to attribute any and all ills to a previous injury, particularly when symptoms emanate from, or near, the site of the injury. The tendency for some injured to exaggerate symptoms for purposes of compensation should not be overlooked. The writer had to testify in many of the above cases as an impartial examiner either at the request of the Government or either side, and he can appreciate the difficulties involved.

*Acknowledgment.* I want to express my gratitude to Dr. S. Paley and his physiotherapy staff for the coöperation in referring most of these cases for cardiac study, and to Mrs. Mary Ball for her help in the electrocardiographic work of this paper.

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# CASE REPORTS

## MYCOTIC ANEURYSM: REPORT OF A CASE*

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Virchow [1] in 1847 described arterial dilatation developing at the site of embolism, and subsequently the rôle of embolism in the production of certain aneurysms came to be generally recognized. The term "mycotic" was adopted to call attention to the etiologic importance of infection. The term is somewhat misleading since a special group of infections has come to be called the mycoses, but it is sanctioned by long and general use.

Mycotic aneurysms are comparatively rare. Any artery may be involved, the aorta most frequently. Mycotic aneurysms usually occur in association with endocarditis lenta. The pathogenesis of the condition may be by (1) the lodgment of infected emboli or bacteria in the lumina of vessels or in the vasa vasorum, or (2) the extension of infection from the aortic or pulmonic valves.

Mycotic aneurysms vary greatly in their appearance, size and other characteristics. As a rule the original embolus cannot be identified. The affected artery shows various degrees of inflammation, destruction, and dilatation with thrombus formation and perhaps healing. Rupture often occurs, leading to free bleeding or the formation of false aneurysms consisting of hematomata which communicate with the lumen of the vessel and which are surrounded by adventitial or perivascular tissue.

The clinical diagnosis of mycotic aneurysms is made only exceptionally. It usually depends on the occurrence of embolism followed by the development of a pulsating tumor.

A patient with a mycotic aneurysm has recently been observed at the Cleveland City Hospital. The case is of interest in that the diagnosis could be made clinically. The process involved the common iliac artery, one not commonly affected.

### Case Report

O. M., a negro, 34 years of age, who entered Cleveland City Hospital August 5, 1940, complained of pain in the right side of the chest. He had had rheumatic fever in 1919 and had been observed periodically since 1934 in the dispensary because of rheumatic heart disease. During the month previous to admission he had fever, sweating at night, malaise, weakness, pain in the chest, and had lost 15 pounds in weight.

Examination showed that the patient was normally developed but poorly nourished and acutely ill. The temperature was 38.5° C., and the pulse rate was 126 per minute. The eye-grounds and conjunctivae were normal. The heart was enlarged, and there was a loud systolic murmur at the apex. The cardiac mechanism was normal and

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the blood pressure was 136 mm. Hg systolic and 74 mm. diastolic. The lungs were normal. The edge of the liver was 1 cm. below the costal margin. No other organs or masses were palpable in the abdomen. There were no signs of myocardial insufficiency.

Roentgenologic examination of the chest showed the left ventricle and pulmonary conus to be enlarged. The erythrocytes numbered 3,500,000 per cu. mm. and the hemoglobin was 9.0 gm. per 100 c.c. of blood. The white blood cell count was 20,000 per cu. mm. The urine contained white blood cells, grade 2, and red blood cells, grade 1. The urea nitrogen was 5.8 mg. per 100 c.c. of blood. Electrocardiograms taken in August and October were normal. Seventeen blood cultures were negative; one taken October 14 revealed the presence of *Streptococcus viridans*.

The condition of the patient became progressively worse. The temperature varied from 37.0° C. to 40.4° C., and chills occurred frequently. On September 4 he complained of pain in the left ankle, and the pulsation of the dorsalis pedis artery on that side was found to be decreased. Petechial hemorrhages in the conjunctivae were present from time to time.

On September 30 he complained of abdominal pain. Examination revealed a tender, pulsating mass approximately 5 cm. in diameter in the lower umbilical region. October 9 the face was edematous and a pericardial friction rub was heard. The urea nitrogen on October 15 was 88.6 mg. per 100 c.c. of blood. The patient died October 15. The clinical diagnosis was rheumatic heart disease, endocarditis lenta due to *Streptococcus viridans*, mycotic aneurysm of the aorta, focal glomerulonephritis, uremia, and uremic pericarditis.

*Autopsy Findings.* (Autopsy performed by Dr. Vladimir M. Sasko.) The body was that of a poorly nourished colored man.

The pericardial sac contained 200 c.c. of yellow-green, clear fluid having a specific gravity of 1.015. The heart weighed 495 gm. The epicardium was normal. There was a recent infarct involving most of the left ventricle and the septum. The mitral leaflets were thickened and firm, and nodular vegetations, varying in diameter from 1 to 20 mm., were attached to the margin of each. The chordae tendineae were thickened and shortened. The other valves showed no endocarditis. Numerous mural thrombi were found in the left ventricle and the right atrium.

The coronary arteries showed very slight sclerosis. In the descending ramus of the left coronary artery, 4 cm. from the ostium, there was an embolus which resembled the vegetations in appearance.

The aorta was normal. The left common iliac artery and the left hypogastric artery were dilated, forming a red-brown, firm, oval-shaped mass measuring 3 by 4 by 5 cm. Upon section, this mass consisted of red-brown, laminated thrombus with a white center. The lumina of the vessels were not occluded.

The lungs showed several septic infarcts and bronchopneumonia. The spleen weighed 95 gm. and was the seat of recent and old infarcts. The kidneys together weighed 470 gm. and contained many infarcts.

Microscopic examination of a section of the occluded coronary artery revealed suppurative arteritis around a thrombus which contained hyaline material similar to that found in the vegetation on the mitral valve. The lesion in the myocardium had all the features of a septic infarct. Sections of the left common iliac and the left hypogastric artery showed the arterial wall and the contained thrombus to be the seat of severe suppurative inflammation. Numerous cocci in chains were present in the sections of the vegetation, the embolus in the coronary artery, the myocardial infarct, and the aneurysm of the common iliac artery. The kidneys showed acute and subacute focal glomerulonephritis. *S. viridans* was recovered from the heart's blood and the vegetations on the mitral valve.

The anatomical diagnosis was chronic rheumatic heart disease, endocarditis lenta

of mitral valve (*Streptococcus viridans*), embolism of the left coronary artery with occlusion of the descending ramus, septic infarct of the left ventricle and septum, and mycotic aneurysm of the common iliac and left hypogastric arteries.

### Comment

The development of a pulsating abdominal tumor in a patient suffering from endocarditis lenta could scarcely be mistaken for any other condition. The associated pain, the rather sudden appearance of the mass, and the occurrence of embolism elsewhere were helpful in arriving at the clinical diagnosis.

### Summary

The appearance of a painful, pulsating abdominal mass in a patient suffering from endocarditis lenta led to the clinical diagnosis of a mycotic aneurysm. Autopsy showed the aneurysm to involve the left common iliac and the left hypogastric artery. The patient also had coronary embolism, with resultant myocardial infarction.

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## CARDIAC ANEURYSM: REPORT OF A CASE WITH CORRELATION OF CLINICAL, RADIOLOGICAL AND ELECTROCARDIOGRAPHIC FINDINGS *

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Until recently cardiac aneurysm, though common at autopsy, has not often been diagnosed clinically.[1] Up to 1930 only 10 cases had been diagnosed premortem.[2] Today, although the diagnosis is by no means commonplace, it is made more and more frequently.

The clinical,[1] radiological,[3] and electrocardiographic [4] features of cardiac aneurysm have been described, but the possibility of diagnosing this condition is not appreciated by most internists and cardiologists.

Because of this condition it was thought desirable to report a case diagnosed clinically as a cardiac aneurysm, and attempt to correlate the clinical, radiological, and electrocardiographic features of value.

### Case Report

The patient came under observation December 12, 1940, because of shortness of breath. For years the patient had had indigestion every spring which lasted a few weeks and then disappeared. About three months previously he had had an attack of indigestion similar to those he had had in the past. These attacks of indigestion were characterized by epigastric pains about two hours after meals, relieved by food. Soon

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after this indigestion began the patient had a very severe attack of pain accompanied by quite a bit of nausea and vomiting, beginning in his epigastrium and radiating to his substernal region and down his left arm. This severe pain lasted six to eight hours and required morphine for relief. Two days later the patient had a similar attack which lasted for only 30 minutes to an hour and was much less severe.† He had had no pain since. Soon after these attacks of pain the patient noticed he had marked shortness of breath, both at rest and on exertion. This was so marked and he became so easily exhausted that it became necessary for him to remain in bed for two months. During this time he had severe palpitation and noted that his heart beat very rapidly. At the time he came under observation he was up several hours a day, and was somewhat better. He still became short of breath on moderate exertion, but there was no orthopnea. The patient's past history was irrelevant. His father and mother were both living, and, although elderly, were in excellent health. The patient smoked in moderation, did not use alcohol, drank one cup of coffee daily.

Physical examination revealed an average white male, 42 years of age, apparently not acutely ill. His blood pressure was 120 mm. Hg systolic and 100 mm.

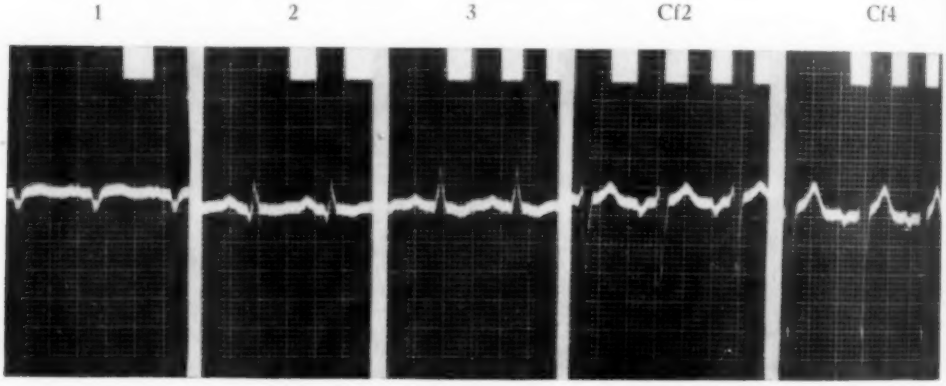


FIG. 1. Electrocardiogram showing right axis deviation.

diastolic, pulse 110, respiration 16. The examination was negative except for the cardiovascular system. There were a few fine râles present at the right lung base. Examination of the heart disclosed the point of maximum intensity to be in the sixth left interspace about 5 cm. outside the midclavicular line. The cardiac impulse extended from mesial to the midclavicular line to the anterior axillary line. It was diffuse and of a somewhat heaving character. The heart was markedly enlarged to percussion; the left border extended about 1 cm. beyond the anterior axillary line. The heart did not seem to be enlarged to the right. On auscultation the heart tones were very poor; both the first and second sounds were diminished in intensity. There was a suggestion of a gallop rhythm along the left sternal border; no murmurs nor adventitial sounds were demonstrable. The liver was palpable three fingers' breadth below the right costal border. Moderate pitting edema of both ankles was present.

The electrocardiogram (figure 1) showed a normal sinus rhythm with a rate of 115, P–R interval 0.16, QRS duration 0.10, right ventricular preponderance, $QRS_1$ notched, $QRS_{2 \text{ and } 3}$ slurred, $Q_2$ present, $T_1$ upright, $T_{2 \text{ and } 3}$ negative, $QRS_{4 \text{ and } 5}$ almost

† Further history obtainable from his physician, Dr. T. H. Rayburn of Pontotoc, Mississippi, was that in October, 1940, the patient was seen with a typical attack of coronary occlusion, characterized by severe pain in precordium, some dyspnea, and some nausea. His blood pressure was 100 mm. Hg systolic and 60 mm. diastolic, and his pulse was barely perceptible at about 100. The pain continued for several days and his disability to date.

entirely down, the first phase of $Cf_2$ being 1½ mm. in height, the first phase of $Cf_4$ being less than 1 mm. in height, S–T–$T_{4 \text{ and } 5}$ normal.

On fluoroscopic and orthodiagraphic examination (figure 2) it was noted that there was moderate congestion in both hilar regions. The apices and the costophrenic angles were clear. The heart was markedly enlarged; this enlargement was of the aortic type, being mostly in the region of the left ventricle. The ratio of the transverse diameter of the heart to the thorax was 70 per cent. In the sagittal view of the chest there was evidence of enlargement in the region of the left ventricle. The aorta measured 3½ cm. in the left oblique view; this is just above the normal limit. Along the left border about 2 cm. above the apex there was a region in which

FIG. 2. Orthodiagram showing elongated apex and area of paradoxical pulsation.

there was no cardiac motility. With the patient turned slightly towards the left oblique diameter there was observed a slight outward bulging of this area with each contraction of the heart.

## DISCUSSION

About 85 per cent of ventricular aneurysms follow cardiac infarction subsequent to the occlusion of a coronary artery.[3] The balance is made up of miscellaneous causes such as syphilis of the myocardium, or is of mycotic, rheumatic, congenital, and traumatic origin.

The pathological changes which occur in the production of a ventricular aneurysm are as follows: Subsequent to an occlusion of a coronary vessel there appears necrosis of the myocardium supplied by this vessel with replacement fibrosis. This weakened area then stretches with the production of a large or small aneurysmal dilatation, depending on the size of the area involved. This

may be saccular in outline, communicating with the ventricular cavity by a neck, or more often a bulge or out-pouching not sharply delineated from the ventricle. An aneurysm may be located in any part of the left ventricle; aneurysms of the right ventricle are very rare, but the most common site is the anterior wall, involving the apex or the left border just above the apex. Other less frequent sites are the posterior wall, base of the heart, or intraventricular septum.[3]

It has been suggested by Brams and Gropper [5] and Fulton [6] that inadequate bed rest predisposes to the formation of ventricular aneurysm, evidently because a firm scar is not allowed to form by the excessive cardiac load subsequent to early return to activity. In the present case the patient attempted to be up some three to four days following his occlusion and was never placed on strict, continuous rest in bed.

Clinically, there is nearly always a past history of coronary occlusion. This is usually clear, as in the case reported, although these aneurysms may occasionally follow a silent occlusion.[3] The length of time for its development varies. The average time of diagnosis in Parkinson and Bedford's [3] series was 17½ months after an occlusion, varying from three months to seven years. Aneurysms occurring a week or two after an occlusion have been reported.[7] In the case reported the diagnosis was made about two and one-half months after a coronary occlusion.

Many signs have been mentioned as having diagnostic significance. Older writers were impressed mainly by such ausculatory findings as murmurs, both systolic and diastolic, and characterized as blowing or whistling, humming or musical. A gallop rhythm was suggestive of this condition to some. These auditory findings have failed to live up to their earlier promise.[1, 5, 3]

An enlarged heart is characteristic, but this alone is without significance unless it occurs in a patient who was previously known to have no cardiac condition that would explain this enlargement. This is true in the present case, and I believe this fact is corroborative evidence that an aneurysm existed in this report.

Pulsatory phenomena have been of great diagnostic significance. Libman and Sacks [8] in 1927 pointed out that a feeble first sound associated with a pulsation most marked between the apex and the sternum was very suggestive of a cardiac aneurysm. A systolic pulsation separate and distinct from the apex pulsation has been stressed by Strauch,[9] Libman and Sacks,[8] Parkinson, Bedford and Thompson.[3] Dressler [1] believes pulsatory findings are of the greatest significance. In his series of cases radiological examination was of help in only one-half of the series, whereas pulsatory phenomena were present in all. He describes these findings as follows: "The diagnosis of cardiac aneurysm is based primarily on physical examination. On palpation one finds a large and forceful cardiac thrust, which, depending upon the site of the aneurysm, is located either within the midclavicular line or outside of it, and most commonly at the level of the fifth rib. The diffuse character of the thrust, its considerable width, and particularly its medial extension, are significant features in diagnosis. The area of pulsation is likely to be situated more craniad than one would expect for the apical thrust caused by an hypertrophied left ventricle. Such a pulsation is of significance for the diagnosis of cardiac aneurysm, if the history and the electrocardiographic findings indicate a preceding cardiac infarction, and if other causes for such a forceful cardiac thrust, such as hypertension or mitral and aortic lesions, can be excluded."

In the present case the area of pulsation was diffuse and of a somewhat heaving character; it extended from the mesial to the midclavicular line to the anterior axillary line. This was in sharp distinction to the very weak heart sounds. Both the first and the second sounds here were equally diminished. Here, too, there was a gallop rhythm, but this is of questionable significance as the patient was in obvious decompensation.

To most men radiography, more especially fluoroscopy, offers the best means of accurately diagnosing cardiac aneurysm.[2, 5, 7, 10]

Parkinson et al.[3] give the following radiographic signs as being of diagnostic significance:

(1) Enlargement of the left ventricle with deformity of its contour.
(2) A localized protuberance inseparable from the heart shadow on rotation of the patient.
(3) Abnormal or absent pulsation of the aneurysmal zone.
(4) Evidence of adhesions between the heart and chest wall.
(5) Calcification of the wall of the sac or contained clot.

The heart is almost always enlarged. This enlargement is left ventricular in type and is of the so-called "aortic contour." The aneurysm most often involves the lower half of the left ventricle, which makes the apex appear broadened or blunted and gives the heart a square or rectangular appearance.[3] The most characteristic finding of aneurysm, when it is present, is an abnormal bulge projecting from the surface of the left ventricular border. This is particularly diagnostic if also there is one of three findings under the fluoroscope:

(1) A diminished or total lack of pulsation in the region of this bulge.
(2) A paradoxical pulsation in the region of this supposed aneurysm, i.e., a systolic expansion of this area.
(3) Calcification of the pericardium or wall of the aneurysm.

A straight anteroposterior view may fail to demonstrate an abnormality of the ventricular contour for several reasons. The aneurysm may grow directly forward[11] or directly backward.[3, 6] If located at the apex, this bulge may be buried in the diaphragm and thus be obscured. Again, the interventricular septum may be involved, and so there would be an internal rather than external aneurysm.[5, 12] For these reasons rotation of the patient into the various oblique positions under fluoroscopic control is invaluable and often will make the diagnosis a certainty, whereas it can only be suspected in the usual A–P radiograph. The right oblique view is best for demonstrating aneurysms of the anterior surface of the heart, the left for lesions on the posterior surface. Parkinson et al.[3] point out that they have been impressed by discrepancy between this enlarged left ventricle and a small vascular pedicle. In other causes of left ventricular hypertrophy, such as hypertension, a large left ventricle is most often associated with a broad pedicle from an unfolding of the aorta.

In the present report fluoroscopy and orthodiagraphy revealed a very greatly enlarged heart. This enlargement was mainly in the region of the left ventricle, which in the A–P view approached the lateral chest wall. The region of the apex was very much elongated. In this area there was a total absence of pulsation. With the patient turned very slightly in the left oblique view there was

seen in this region a slight outward bulging with each systolic contraction of the heart.

The electrocardiograph has been thought by many to give little diagnostic aid,[1, 3, 5, 6] being only of corroborative value in that it showed evidence of cardiac infarction and helped in the location of the area infarcted.

In 1938 Sigler and Schneid [10] pointed out that typical aneurysms seemed to be associated with major QRS deflections directed downward in the second and third lead with low voltage in Lead I. Nordenfelt [13] in 1939 made a study of electrocardiographic changes associated with ventricular aneurysms, collecting eight cases from the literature and reporting two of his own. He concluded "that large chronic aneurysms of the anterior wall of the ventricle often give the following electrocardiographic changes: Relatively low $R_1$, deep $S_2$, $S_3$, elevated S–T segments in all leads, negative $T_1$, and positive $T_2$, $T_3$. There is often also a $Q_1$. In four cases Lead IV was also included; in those cases R was absent and the S-wave was deep. The S–T segment was elevated and passed directly into a positive T-wave." He also found this was a relatively rare type of electrocardiogram, occurring only four times in 1300 tracings, and, apart from aneurysms, was found only with anterior infarcts in the process of healing. If persistent, it is always suggestive of cardiac aneurysm. Eliaser and Konigsberg [4] in the same year confirmed that this type of electrocardiogram was found in the presence of ventricular aneurysm, finding it in 40 per cent of their cases and in 35.3 per cent of cases reported in the literature. They also described a second type of electrocardiogram which, though rare in occurrence, was just as diagnostic as the above. In cases collected from the literature this was found in 23.5 per cent, whereas in their series it occurred in 40 per cent. This type of curve is described as showing marked right axis deviation with a negative T-wave in Lead I and an upright P in the same lead. These authors were unable to establish any correlation between the location of the aneurysm of the left ventricle and the axis deviation produced on the electrocardiogram. Aneurysms of the same site might produce any one of a number of electrocardiographic changes, namely (1) an $S_1$ type, (2) an $S_{2, 3}$ type, (3) bundle branch block, and (4) miscellaneous changes.

In the case reported the electrocardiogram was essentially similar to the $S_1$ type as reported by Eliaser and Konigsberg.[4] Here, however, $T_1$ was positive, whereas $T_{2 \text{ and } 3}$ were slightly negative. There was also a small Q-wave in Lead II.

The presence of right axis deviation in the electrocardiogram in a case with obvious left ventricular enlargement is interesting enough to deserve comment. It is rare to find right axis deviation in the presence of hypertensive or arteriosclerotic heart disease. Nathanson [14] found only slight right axis deviation in two cases out of a group of 50 with advanced coronary disease. White and Comeau,[15] in 200 cases of coronary artery disease, found only seven (3.5 per cent) to have right axis deviation, and here it was of a very slight degree. They concluded: "It is evident that the finding of right axis deviation is strong, though not conclusive, evidence that the patient does not have coronary heart disease."

Bohning and Katz [16] found right axis shift to be infrequent in coronary occlusion, occurring only in some cases of anterior infarction. McMillan and Bellet [17] state that "right axis deviation sometimes occurs after an anterior in-

farction." Klainer,[18] in a recent report, found only 36 instances of right axis deviation in hypertensive or arteriosclerotic heart disease in all the electrocardiographic records of the Beth Israel Hospital over a 10 year period (1929–1938). Of the 13 autopsied cases 12 showed severe coronary disease, and in 10 there were myocardial infarcts. In all of these cases showing infarcts there was extensive necrosis of the heart muscle of the left ventricle. In two other cases there was a diffuse fibrosis of the myocardium. The cause of this right axis deviation in the presence of left ventricular enlargement, Klainer believed, was due to the widespread necrosis of the left ventricle so interfering with the conduction system of the myocardium as to completely nullify the effects of hypertrophy of this ventricle. No mention is made in this article as to whether a ventricular aneurysm was present or not. However, if the necrosis of the myocardium was extensive, as the author states, it is highly probable that aneurysmal dilatation was present to a greater or lesser extent in some of his cases.

In view of the rarity of occurrence of right axis deviation in cases with hypertensive or arteriosclerotic heart disease and of its frequency (40 per cent of cases, Eliaser and Konigsberg [4]) in cardiac aneurysm, I believe this type of electrocardiogram is very suggestive of a cardiac aneurysm, and when it occurs unexpectedly in a case of otherwise unexplainable left ventricular enlargement the possibility of this diagnosis should be brought to mind.

The $S_{2, 3}$ type, although also suggestive of ventricular aneurysm, occurs not infrequently in other conditions, such as non-sacculated myocardial infarcts, dilated hearts, and marked enlargement of the left ventricle.

As Eliaser and Konigsberg [4] point out, it is worthy of note that 63.7 per cent of cardiac aneurysms fall into one of two electrocardiographic patterns.

## Summary

1. A case of cardiac aneurysm is reported with clinical, radiological, and electrocardiographic findings.

2. No one method will diagnose every case, but the majority of cases can be diagnosed antemortem by the correlation of the above methods.

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## VISUALIZATION OF THE BILIARY TRACT WITH AIR AND BARIUM FOLLOWING A BARIUM MEAL *

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During studies made on the gastrointestinal tract, it has been noted from time to time that the gall-bladder or bile ducts, or both, contain air or barium. There has been much speculation about the cause of these occasional findings and an even greater interest as to the relationship between such findings and the symptoms presented by the patient. The cases reported are far from being identical and opinions differ greatly as to the cause.

In 1901, Stolz [1] reported three cases in which gas was found in the gall-bladder at autopsy. In 1925, Kirchmayr [2] reported an emphysematous cholecystitis diagnosed during a cholecystectomy. In 1927, Wahlberg [3] reported four cases of gas bacillus infection found in a thousand gall-bladder operations. He included two cases previously reported in 1923 by Brutt. In 1931, Hegner [4] reported a case of gaseous pericholecystitis due to gas bacillus infection. The primary pathological process was a chronic cholecystitis with stones.

Gabriel,[5] in 1930, reported proof of patency of the common bile ducts in a case operated upon twice. The first operation was cholecystectomy. The patient's general condition had not permitted the removal of the gall-bladder at the first operation, at which time the gall-bladder had contained much foul pus. A large stone was found in the common bile duct when the gall-bladder was finally removed. Patency was demonstrated by injection of lipiodol through a tube inserted into the ducts through the biliary fistula.

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In 1931, Jenkinson and Brouse [6] reported two cases in which there was visualization of the bile ducts by barium administered for gastrointestinal study. They mentioned 10 such cases reported at that time, most of which were explained on the basis of intestinal fistulae between some part of the gastrointestinal and the biliary tract.

In 1933, Rees [7] reported a case of duodenocolic fistula with incompetent sphincter of Oddi. Traction from the fistulous tract apparently produced the incompetency, allowing the duodenal contents to pass into the bile ducts. The ramifications of the hepatic tree were visualized by a barium meal. Liver function was normal, but a non-functioning gall-bladder was demonstrated. An exploratory laparotomy was performed, revealing a fistula from the descending portion of the duodenum to the transverse colon. The fistula was dissected and removed. The gall-bladder was opened and gas escaped. Symptoms were relieved. However, a barium meal later still demonstrated patency of the sphincter of Oddi with barium filled bile ducts.

In 1936, Powers [8] reported four cases with air in the hepatic ducts. He states that air shadows in the hepatic tree probably occur quite frequently. It appears to be his impression that internal biliary fistulae were responsible for the findings in his cases. In 1938, Schmidt [9] reported a case of emphysematous cholecystitis. The gas-filled gall-bladder was shown on roentgen examination, without the use of dye. The cholecystogram showed poor gall-bladder function. This case was treated medically with improvement.

In 1921, Busi [10] reported two cases with the gall-bladder filled with barium and air, following a barium meal. In both cases there was a spontaneous biliary fistula between the gall-bladder and the duodenum, following a rupture of the gall-bladder, with passage of a biliary calculus directly into the duodenum.

In 1925, Berg [11] reported a case with air and barium in the gall-bladder after a barium meal, six years following a surgical anastomosis of the gall-bladder to the stomach for an unstated reason.

In 1926, Mallet [12] reported three cases in which both barium and air were present in the gall-bladder following a barium meal. The first was a case which had been operated upon for cholelithiasis and chronic pancreatitis, in which a surgical anastomosis had been performed between the gall-bladder and stomach three years previously. In his second case an anastomosis had been performed a month and a half previously between the gall-bladder and stomach because of obstructive jaundice caused by a tumor of the pancreas. In the third case, an anastomosis between the gall-bladder and stomach had been performed for the relief of painful abdominal crises. In this last case roentgenograms seven months later showed air in the gall-bladder, with barium in the region of the anastomosis.

Alberti,[13] in 1927, reported a case in which a fistulous tract had been formed between the duodenal bulb and the gall-bladder, following a periduodenal abscess subsequent to the perforation of a duodenal ulcer. Air and barium were seen in the fistulous tract, the gall-bladder and the intra- and extrahepatic bile passages following a barium meal.

In 1931, Gråberger [14] reported the case of a 70 year old female who had suffered from abdominal pain associated with eructations of gas for 30 years. An internal biliary fistula between the gall-bladder and the duodenal bulb was found, which was believed to have been caused by the passage of a calculus from

the gall-bladder into the duodenum. In this case the smaller biliary radicals in the liver were outlined with the barium, and air noted in the smaller biliary ducts in the liver. No air was seen in the gall-bladder.

Beutel,[15] in 1932, reported a case having adenocarcinoma, Grade IV, of the gall-bladder with cholelithiasis, and associated jaundice. There was a fistula between the gall-bladder and the duodenum, and air was noted in the gall-bladder. The patient died and the findings were confirmed.

Prévôt,[16] in 1933, reported a case in which there was a spontaneous biliary fistula between the gall-bladder and the hepatic flexure of the colon, caused by the direct passage of a stone from the gall-bladder to the colon. In this case, following a barium enema, the barium was seen in the fistulous tract, and both barium and air in the gall-bladder. Air was also noted in the common bile duct and the hepatic duct. Prévôt reported a second case the same year in which a gastrointestinal series showed barium in the gall-bladder and cystic duct, with air in the common bile duct, in a patient who had a spontaneous biliary fistula from the gall-bladder to the duodenum. This followed a direct passage of a stone from the gall-bladder into the duodenum.

In 1935, Podlasky [17] reported a case in which there had been interscapular pain, with vomiting for one year, and a period of similar type of pain lasting two months, 15 years previously. Films after a barium enema and a barium meal both showed barium and air in the gall-bladder. A fistula was demonstrated between the fundus of the gall-bladder and the hepatic flexure that had probably occurred as a result of the direct passage of a stone from the gall-bladder to the colon. Operation was performed, with the removal of the fistulous tract, and a stone from the gall-bladder. The patient died postoperatively.

In 1939, Pfeile [18] reported a case in which only air was seen in the gall-bladder. This patient had had a surgical anastomosis of the gall-bladder to the duodenum because of a carcinoma of the ampulla of Vater.

It will be noted that in these cases the appearance of air in the gall-bladder was due either to a gas bacillus infection of the gall-bladder, or to a fistulous communication from the biliary tract to the stomach, the duodenum, or the colon, either spontaneous or surgical in origin. Numerous instances are found in the literature in which the biliary tract in part or as a whole has been outlined with barium following a barium meal or a barium enema, but without air being noted in the biliary tract. In these cases spontaneous or surgical biliary fistulae were present in the great majority. In many instances there had apparently been a direct passage of a calculus from the gall-bladder to the duodenum, either the duodenal bulb, or the second portion of the duodenum, or to the colon, most commonly the hepatic flexure. Seventeen cases have been reported in which no fistulae were demonstrated, and in which the biliary tract was outlined with barium to a greater or lesser extent. In none of the cases without fistulae was there any air noted in the gall-bladder or the bile ducts. It is believed in these cases that the barium gained entrance into the biliary tract through an incompetent sphincter of Oddi, and perhaps this incompetency accounted for the symptoms in these cases.

The first reported case of this type was in 1921, when Stephenson [19] reported a case with epigastric pain, relieved by food, of 18 years' duration. A previous cholecystectomy and appendectomy had been performed. Again, in 1921, Beall and Jagoda [20] reported a case that had had epigastric pain, nausea and vomiting,

with chills and associated fever, for four months. There had been no previous operation. Exploration revealed an abscess in the left upper portion of the lesser peritoneal cavity, and enlargement of the pancreas was noted. In both of these cases there was visualization of the biliary tract with barium following a barium meal, but no fistulae were found.

In 1926, Fishbaugh [21] reported a case, with nausea and vomiting of a few months' duration, associated with loss of weight. The patient died and at autopsy a tumor of the pancreas was found obstructing the second portion of the duodenum. Sighinolfi,[22] in 1926, reported a case in which the chief symptoms had been epigastric pain, with nausea and vomiting for two to three years. No operations had been performed. No fistulae were demonstrated in either of these cases.

In 1929, Venable and Briggs [23] reported two cases in which there was visualization of the biliary tract without a fistula. The first complained of pain, vomiting, chills and fever. This patient had had a previous cholecystectomy, and operation subsequent to the examination was performed with removal of a calculus from a greatly distended common bile duct. The second case complained of pain, nausea and vomiting, with loss of weight. Previously a tumor, which had involved the greater curvature of the stomach, had been removed from the splenic flexure of the colon. Operation was again performed and a tumor mass involving the greater curvature of the stomach, the jejunum, the spleen, and the pancreas was found.

In 1929, Johannesson [24] reported two cases in which there was incompetency of the sphincter of Oddi. There had been no previous operations in these cases. A large calculus was removed from the common bile duct, in one case, and the gall-bladder was removed because of chronic cholecystitis in the other. In the latter case, the common bile duct was large and the walls thick.

In one of the cases mentioned by Jenkinson and Brouse,[6] in 1931, no fistula was demonstrated. It is assumed that there was incompetency of the sphincter of Oddi. This patient had had a cholecystostomy 17 years previously, later an appendectomy, removal of calculi from the pancreas, and an oöphorectomy. She had had jaundice four years previously, associated with pain in the right upper quadrant of the abdomen. No subsequent operation was performed.

In 1932, Pennington [25] reported a case that for one year had suffered from attacks of abdominal distention with nausea and vomiting, and loss of weight. Operation was performed, and a carcinoma of the pancreas, with moderate dilatation of the first portion of the duodenum and narrowing of the transverse portion of the duodenum, was found.

In 1934, Béclère and Porcher [26] reported a case with the common bile duct, cystic duct, part of the hepatic duct, and the gall-bladder visualized with barium, following a barium meal. There was marked antiperistalsis in the descending and ascending portions of the duodenum, and a fistula was not demonstrated.

In 1935, Levy et al.[27] reported a case with visualization of the extra-hepatic ducts and gall-bladder with barium, in a patient who had complained of epigastric pain for 10 years. Operation revealed a duodenal ulcer but there was no fistula.

In 1936, Titone [28] reported a case with epigastric pain, on whom previous gastroenterostomy had been performed. At operation a duodenal ulcer was found, with dilatation of the first and second portions of the duodenum.

In 1937, Wichtl [29] reported a case with pain in the right upper quadrant, chills

and fever one year previously. At operation a scar of a duodenal ulcer in the region of the ampulla of Vater was found. The scar was located on the anterior wall of the descending portion of the duodenum, the entire duodenum being infiltrated, and the posterior wall fixed to the pancreas. It was believed that the contraction of the scar distorted the ampulla of Vater so that the sphincter of Oddi became incompetent.

In 1938, Cristofanetti [80] reported four cases in which there was visualization

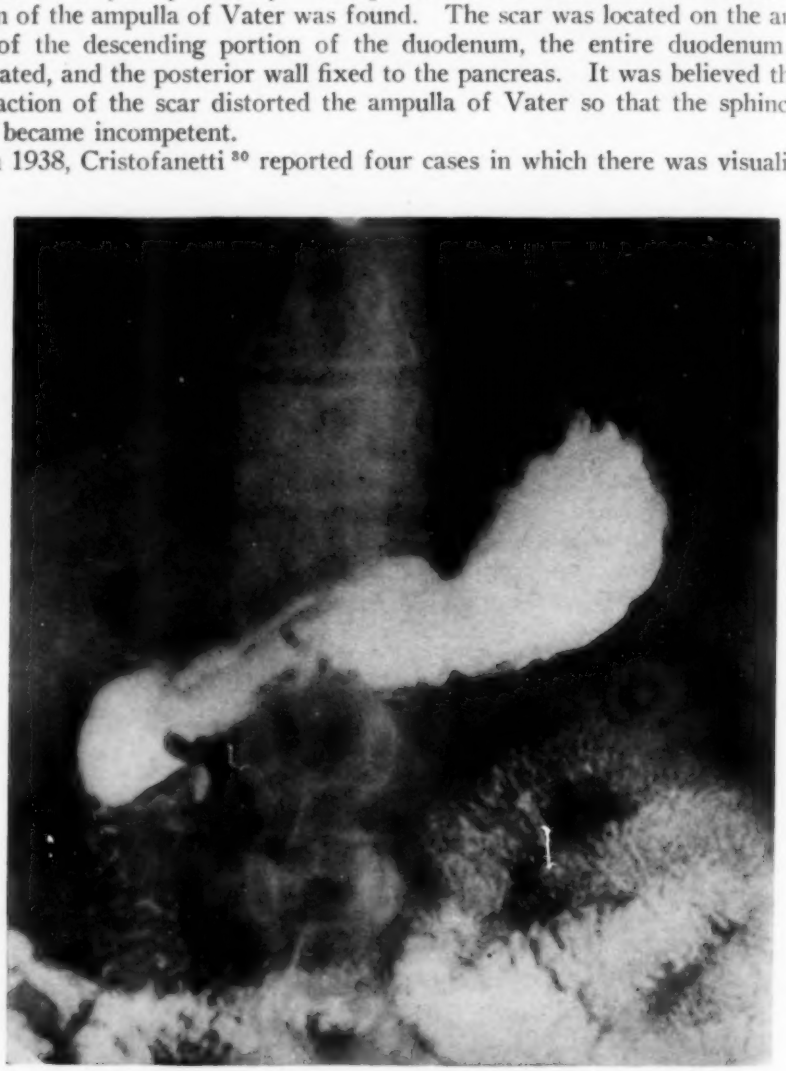

FIG. 1. Gastrointestinal series, showing air, with a small amount of barium, in the gall-bladder.

of the biliary tract. In three cases fistulae were found, and in the fourth there was none. The chief complaint of this case was epigastric pain. The gall-bladder was not visualized with the dye, and a diagnosis of chronic cholecystitis was made.

In cases without fistulae, as with those with fistulae, the symptoms varied, but in most instances were referred to the upper abdomen. A variety of conditions was found in the cases with incompetency of the sphincter of Oddi, the most frequent being duodenal ulcer and tumors in the upper abdomen. No

definite conclusions can be drawn from this small group of cases. In the case we are reporting the findings cannot be explained by either a gas bacillus infection of the gall-bladder or a fistula between the biliary and gastrointestinal tracts. There was undoubtedly a relaxation of the sphincter of Oddi with general atony of the biliary tract. No case has been found in the literature in which the biliary tract has been visualized, and air seen in the gall-bladder without a fistula being present, as was in the case reported below.

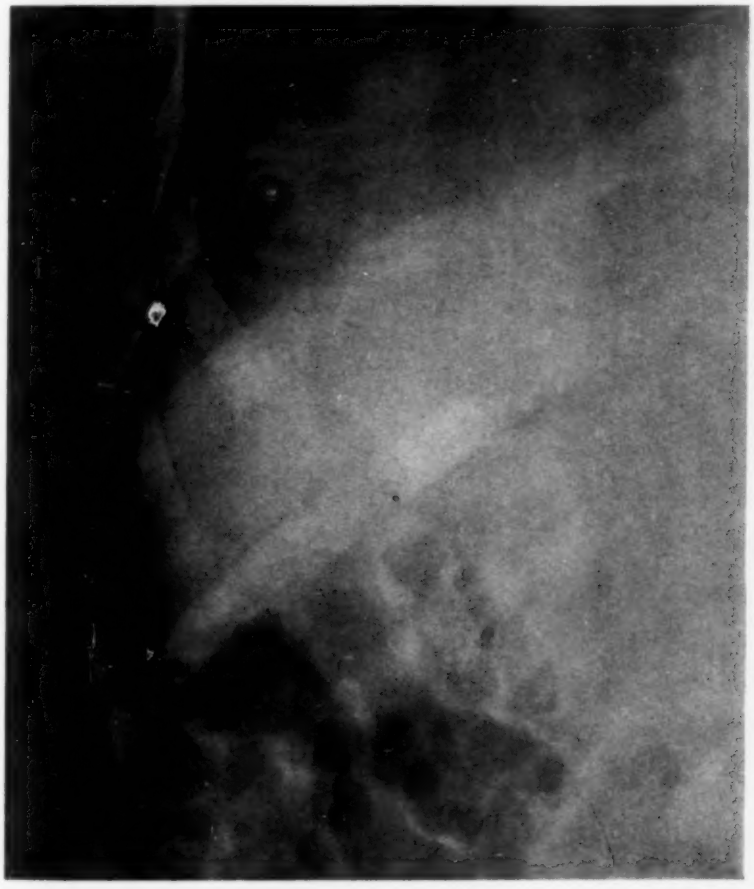

FIG. 2. Fourteen-hour cholecystogram showing the dye and air in the gall-bladder.

## CASE REPORT

E. J. M., male, aged 46 years, was admitted to Walter Reed General Hospital on December 26, 1939. His previous personal history was not remarkable until 1930. At that time, following symptoms of gaseous distention, burning epigastric pain before and one hour after eating, a diagnosis of gastric ulcer had been made. Following dietary measures in 1931, a gastrointestinal series showed no recurrence of the ulcer. Four years prior to admission he developed pain in the right upper quadrant associated with flatulence occurring in paroxysms. A cholecystogram in 1938 showed a non-

functioning gall-bladder without calculi. Symptoms had continued, but had been worse for a few weeks prior to admission. Ten days prior to admission he had had a severe attack of pain in the right upper quadrant with marked flatulence, and similar attacks almost daily for a week prior to admission. The pain radiated to the back and to the area below the right shoulder. The severity of the pain varied, but was

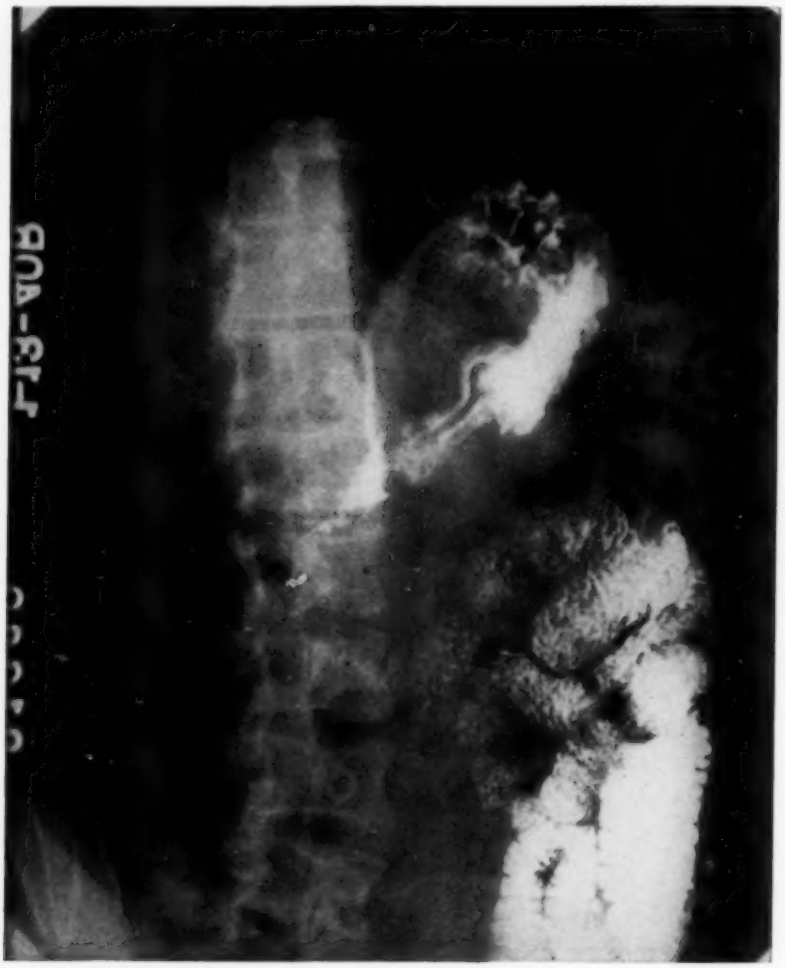

FIG. 3. Combined cholecystogram and gastrointestinal series, taken prior to operation, showing air and barium in the gall-bladder, and barium in the common bile duct, hepatic ducts and the smaller bile ducts in the liver.

often excruciating. It occurred most often when the stomach was empty, often waking the patient at night. The pain was relieved by alkalies, but best by milk. The pain frequently seemed to be brought on by beer or a fatty meal. There had been vomiting on only one occasion, and that occurred during a severe attack of pain 10 days prior to admission. There had been no nausea. The stools had occasionally been light in color, but not clay-colored at any time. He had been eating a moderately low fat diet for some months, and had drunk no alcoholic beverages.

Examination showed a well nourished adult male weighing 165 pounds. Aside from moderate tenderness in the upper right and lower left quadrants of the abdomen, the examination was normal.

Urinalyses and repeated blood counts were normal. The Kahn test was negative. The blood urea nitrogen rose to 33 mg. per 100 c.c., following the vomiting of about 200 c.c. of old and fresh blood on January 13, 1940. The creatinine was 2 mg.

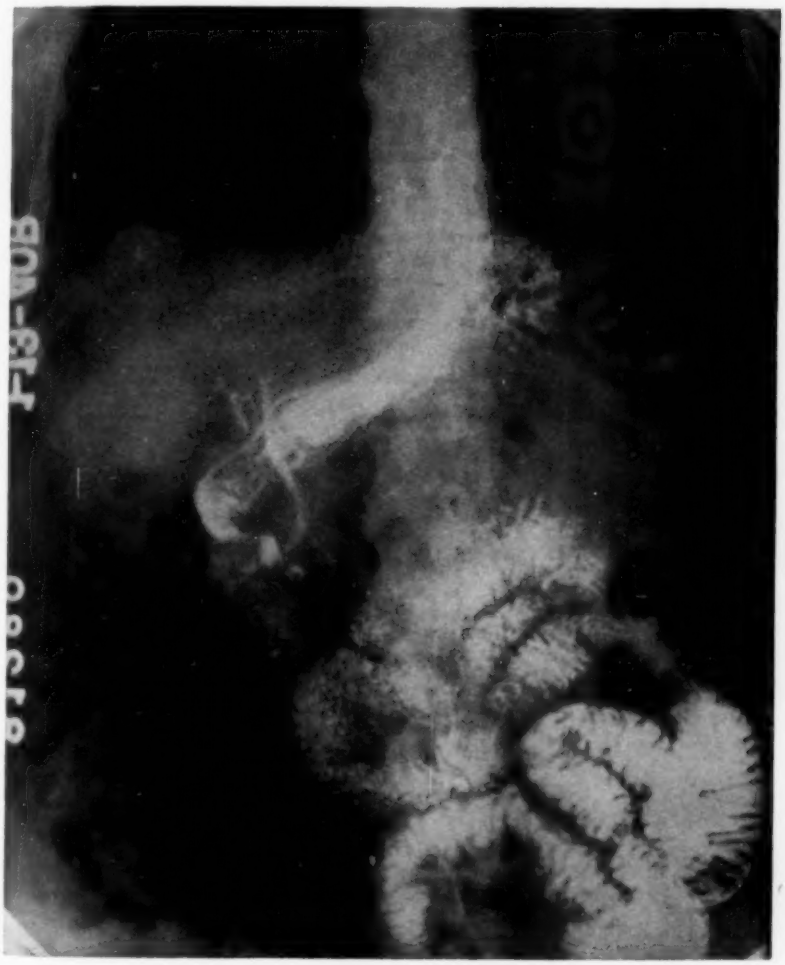

FIG. 4. Combined cholecystogram and gastrointestinal series, taken prior to operation, showing the dye and air in the gall-bladder, and visualization of the biliary tree with barium.

per 100 c.c. The blood chlorides were normal. Six days after the hemorrhage from the gastrointestinal tract, the blood urea nitrogen had returned to normal. Proctoscopic examination was normal. Gastric fractional analysis showed a high terminal acidity. Repeated studies of the gastrointestinal tract following a barium meal, alone (figure 1), and combined with a cholecystogram (figures 2, 3 and 4) revealed a constant deformity of the second portion of the duodenum, associated with a reflux of

the opaque material into the common, cystic, hepatic and pancreatic ducts, and the gall-bladder. The gall-bladder was outlined by the dye, and showed a fluid level and the presence of air (figures 2 and 4). At six hours a small amount of barium remained in the gall-bladder and common ducts.

The cause of the findings was not determined, but it was felt that there might possibly be a duodenal ulcer, or a polyp in the second portion of the duodenum in the region of the sphincter of Oddi, which might account for its incompetency. Because of this possibility and the gastrointestinal hemorrhage, an exploratory laparotomy was

FIG. 5. Combined cholecystogram and gastrointestinal series, following operation, still showing visualization of the biliary tree with barium.

performed on January 17, 1940. The stomach was found to be normal. The duodenum was opened and explored for a distance of eight inches, and no polyp, tumor or ulcer was found. A large tube passed easily, without obstruction, through the first and second portions of the duodenum and no abnormalities were found. The gall-bladder was adherent to the second portion of the duodenum and was easily freed. No stones were palpable and the walls of the gall-bladder were not thickened. The common bile duct was easily palpated and no stones felt. The head of the pancreas was somewhat larger and firmer than normal, but a diagnosis of tumor of the head of the pancreas could not be made on gross appearance. Following operation a bland

diet was taken and symptoms improved. No further acute pain or distress was experienced.

On February 13, 1940, a combined cholecystogram and gastrointestinal series (figures 5 and 6) showed the same findings that were present prior to operation. The patient was discharged from the hospital on February 19, 1940, and has continued to be free from acute pain and flatulence to date (April 30, 1940).

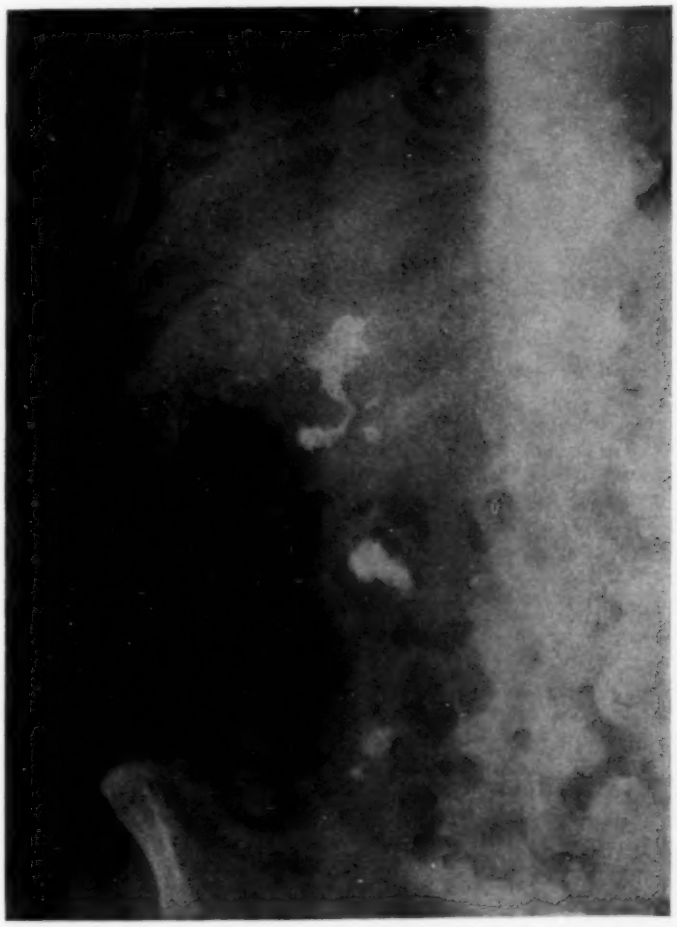

FIG. 6. Combined cholecystogram and gastrointestinal series at six hours, showing faint visualization of the gall-bladder with the dye, and a fleck of barium retained, and streaking of the intrahepatic ducts with barium, taken following operation.

## COMMENT

The findings in the case reported were undoubtedly caused by incompetency of the sphincter of Oddi, with a general atony of the whole biliary tract. Traction from the cholecystoduodenal adhesions may have played a part in producing the incompetency of the sphincter of Oddi. Releasing the adhesions at operation followed by the use of a bland diet, low in fat, may in part explain the symptomatic relief afforded this patient.

SUMMARY

1. The literature on emphysema of the gall-bladder, and visualization of the biliary tract with barium following a barium meal, is briefly reviewed. Previously reported cases were explained on a basis of a cholecystitis due to gas bacillus infections, to internal biliary fistulae, or, as in the case reported, to incompetency of the sphincter of Oddi.

2. A case of emphysema of the gall-bladder with incompetency of the sphincter of Oddi, and general atony of the biliary tract, which was visualized following a barium meal, symptomatically relieved by the release of cholecystoduodenal adhesions, and dietary measures postoperatively, is reported.

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# EDITORIAL

## *HEPATITIS FOLLOWING THE ADMINISTRATION OF HUMAN SERUM*

THE first clear recognition of the association of hepatitis and jaundice with the administration of supposedly normal human serum appears to have been made by Findlay and MacCallum,[1, 2] who reported the development of this condition in men who had received yellow fever vaccine. They proved that the disease so produced was not yellow fever and that the active agent could have been conveyed only by the human serum used in the cultivation and preparation of the vaccine.

A little later Soper and Smith [3] reported the occurrence of similar cases in Brazil, and in 1940 Fox et al.[4] reported a second outbreak. A large proportion of the cases of jaundice was limited to those who received vaccine from three lots out of 265 which had been used during that period. As far as known these lots differed only in the source of the human serum used in their preparation.

A large number of similar cases also occurred in the armed forces of the United States in 1942.[5, 6] The Secretary of War announced that 28,585 cases of jaundice occurred with 62 deaths in all. Here, too, jaundice occurred only after the administration of certain lots of vaccine, and it was believed that the noxious agent was introduced in the human serum.

In 1937, an outbreak of jaundice occurred in England among children who had received injections from one batch of pooled convalescent measles serum. Details of this epidemic have recently been published.[7] Of 109 cases treated with this lot, 41 developed hepatitis and eight died. A second batch of adult measles serum gave rise to at least 11 cases of hepatitis with one death. Although differing in some details, the disease so closely resembled that following yellow fever vaccine that it seems probable that a similar if not identical agent is concerned.

A brief reference [7] is also made to a similar apparently milder epidemic of 86 cases of jaundice which developed in 266 British troops after the administration of Seitz-filtered pooled mumps convalescent plasma.

One striking feature of all these outbreaks was the long incubation period. This ranged from 12 to 20 weeks in a large majority of the cases, with ex-

[1] FINDLAY, G. M., and MACCALLUM, F. O.: Note on acute hepatitis and yellow fever immunization, Trans. Roy. Soc. Trop. Med. and Hyg., 1937, xxxi, 297–308.

[2] FINDLAY, G. M., and MACCALLUM, F. O.: Hepatitis and jaundice associated with immunization against certain virus diseases, Proc. Roy. Soc. Med., 1938, xxxi, 799–806.

[3] SOPER, F. L., and SMITH, H. H.: Yellow fever vaccination with cultivated virus and immune and hyperimmune serum, Am. Jr. Trop. Med., 1938, xvii, 111–134.

[4] FOX, J. P. ET AL.: Observations on the occurrence of icterus in Brazil following vaccination against yellow fever, Am. Jr. Hyg., 1932, xxxvi, 68–116.

[5] Jaundice following yellow fever vaccination, editorial, Jr. Am. Med. Assoc., 1942, cxix, 1110.

[6] The outbreak of jaundice in the army, Circular letter No. 95, S. G. O., Jr. Am. Med. Assoc., 1942, cxx, 51–53.

[7] Homologous serum jaundice, Memorandum prepared by medical officers of the Ministry of Health, Lancet, 1943, i, 83–88.

tremes ranging from two weeks to over a year. In most other respects the disease was indistinguishable from ordinary infectious hepatitis (catarrhal jaundice), either in its clinical features or in the pathological lesions reported in the fatal cases.

The onset was usually gradual, with malaise, fatigue, loss of appetite and digestive disturbances; distention, epigastric distress, nausea, vomiting and diarrhea or constipation were frequently observed. Fever was slight and often absent. The urine became dark and the feces often light in color. Pruritus occasionally preceded the appearance of icterus. This was usually moderate in intensity and in a few cases failed to develop. The blood serum showed a high icterus index and gave usually a positive direct van den Bergh reaction.

In some cases there was pain and stiffness in the joints, and rashes appeared, urticarial in type or resembling erythema multiforme. In about 20 to 30 per cent of the cases the liver was enlarged and tender, but demonstrable enlargement of the spleen was rare. The leukocyte count was usually normal. Bromsulfalein retention was commonly observed during the acute stage in the cases so tested, but the excretion rate returned to normal with recovery.

In the children who had received measles convalescent serum, the disease was relatively severe and the mortality high. In the severe cases there was often restlessness, irritability, intractability with screaming or delirium, occasionally muscular rigidity with convulsions, or flaccidity; and disturbance of reflexes, including an extensor plantar response. These features suggest an associated encephalitis, although the spinal fluid was normal in the one case examined.

A majority of the cases recovered in from four to eight weeks, and recovery seems to have been complete. In the fatal cases, death usually occurred from three to six weeks after the onset of the illness with extreme limits in the yellow fever vaccine cases of 2 to 12 weeks. Four of the measles convalescent serum cases, however, died on the fourth, fifth, sixth and ninth days respectively. The mortality varied from 0.2 per cent in the U. S. Army cases and 2.4 per cent in the Brazilian cases of Fox et al., to 12 per cent in the small group receiving measles convalescent serum.

The principal autopsy finding was necrosis of the liver parenchymal cells, beginning in the center of the lobules and progressing in the extreme cases to the usual picture of acute yellow atrophy. Edema and acute inflammation of the gastrointestinal tract, particularly of the cecum, were mentioned in the American Army cases.

The etiology of the hepatitis is a question of great interest which has not yet been solved. Numerous attempts to isolate an infectious agent by culture and animal inoculation have been unsuccessful. Findlay and MacCallum suggested that the agent is a virus. This was based in part on the fact that it passed through a Seitz filter, that it perpetuated itself in the cultures of vaccine, and resisted inactivation (and in the case of the measles serum, treat-

ment with phenol and ether). Because of the clinical resemblance of postvaccination jaundice to infectious hepatitis, they suggested that the latter disease is caused by a virus and that the serum used in preparing the vaccine may have come from a subclinical case of hepatitis (or possibly a carrier).

There is no direct proof of this hypothesis, nor is it known that infectious hepatitis is caused by a virus. No donor of icterogenic serum has been reported, who gave a history of jaundice. Three positive objections to this theory have been advanced. The incubation period of the two diseases is quite different. That of infectious hepatitis is believed to be usually between two and four weeks, whereas that of "serum jaundice" is as many months. The age incidence is also different. A majority of the cases of infectious hepatitis occur in children or adolescents under 16. In the Brazilian cases, however, adults were predominantly affected, and suffered a more severe form of the disease than did children.

Finally, if serum hepatitis is identical with infectious hepatitis, there should be contact infections in persons who had been exposed to cases of serum hepatitis. This has not been the experience either in Brazil or in the U. S. Army. Propert, however, has reported two cases of jaundice in contacts with cases of measles serum hepatitis. Furthermore Findlay and Martin [8] mention the occurrence of a disease indistinguishable from infectious hepatitis in African personnel in a unit in which they had been exposed to British troops with postvaccine jaundice.

Attempts have been made to convey infectious hepatitis to human volunteers, but the results have been conflicting. Thus Voegt [9] claims to have transmitted the disease to human volunteers by feeding duodenal contents and by injections of serum from patients in the preicteric stage. Lanier,[10] on the other hand, reported negative results in a similar series of experiments. Attempts to transmit the disease to animals have been almost invariably unsuccessful.

Findlay and Martin,[8] however, have recently reported transmission experiments in which they inoculated four volunteers intranasally with nasal washings from four cases of jaundice following yellow fever vaccine. After an incubation period of 28 to 50 days, a mild hepatitis developed in three of the four subjects. This observation, which appears to be dependable, confirms the view that a living agent is concerned, although it does not prove the identity of serum jaundice and infectious hepatitis.

This whole question is under active investigation, and a solution of many of these points may be anticipated. As far as vaccination against yellow fever is concerned, from the practical standpoint the difficulty has probably been met simply by discontinuing the use of human serum in preparing the vaccine.

[8] FINDLAY, G. M., and MARTIN, N. H.: Jaundice following yellow fever immunization. Transmission by intranasal instillation, Lancet, 1943, i, 678–680.

[9] Voegt, quoted by Findlay and Martin.[8]

[10] Lanier, quoted by Fox et al.[4]

The cases of jaundice which were first recognized all followed the use of serum for purposes of immunization. This is doubtless merely because their epidemic occurrence arrested attention and made it relatively easy to find a common factor which could explain their origin. There is no reason to doubt that cases of jaundice would occur if blood from such donors were used for ordinary transfusions or for the preparation of pooled plasma or serum. The long interval of two to six months before the development of the jaundice would divert suspicion from the transfused blood as a cause of the illness unless the possibility of such a relationship were known to the observer. The first clearly recognized cases of this type were reported from a British hospital.[7] Of 36 patients receiving massive transfusions of Seitz-filtered dried human serum in the treatment of peripheral vascular disease, eight developed jaundice. Conditions were such that ordinary infectious hepatitis could be excluded. Beeson [11] has also reported seven cases of jaundice occurring one to four months after transfusions of blood or plasma. Six of these occurred among a group of 81 persons diagnosed as catarrhal jaundice or toxic hepatitis.

With the current widespread use of plasma, cases of this type are certain to develop. Prevention at present is a difficult problem, as no experimental animal is known to be susceptible to the agent. A preliminary trial of each lot of pooled plasma in a small group of human subjects would presumably determine its safety. Because of the long period of observation, however, such a procedure would scarcely be practicable under field conditions. Fortunately the incidence of such cases is small, the mortality is low and recovery appears to be complete. The risk involved is too small to restrict the use of blood or plasma in any conditions in which it is needed.

[11] BEESON, P. B.: Jaundice occurring one to four months after transfusion of blood or plasma, Jr. Am. Med. Assoc., 1943, cxxi, 1132–1134.

# REVIEWS

*Dermatologic Therapy in General Practice.* Second edition. By MARION B. SULZBERGER, M.D., and JACK WOLF, M.D. 632 pages; 21 × 14.5 cm. Year Book Publishers, Chicago. 1942. Price, $5.00.

This book is intended primarily for general practitioners, and the authors give a clear, concise expose of the commoner diseases of the skin. In addition to the general principles of therapy, the authors give detailed formulae for many of the diseases and indicate how the substances are to be used. There are a few photographs illustrating methods of therapy and skin lesions which are quite helpful.

Although the title of this book is "Dermatologic Therapy," the authors include in it a chapter on syphilis. Since any scheme for the treatment of syphilis must at present be tentative and incomplete, because ideas and methods are changing as a result of current research, the chapter is satisfactory, although necessarily brief. The book as a whole can be highly recommended for general practitioners and students entering practice.

H. M. R.

*Occupational Diseases of the Skin.* By LOUIS SCHWARTZ, M.D., and LOUIS TULIPAN, M.D. 799 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, $10.00.

Since occupational diseases have been recognized by almost all states in the Union as a cause for compensation, numerous articles and symposia on the subject have been published. The culmination of these may be found in this book by Schwartz and Tulipan, in which the authors have thoroughly reviewed the entire subject and have included essentially all the ordinary occupations and their hazards.

Among the more timely chapters are those on dermatoses caused by explosives and war gases. Seventy-four occupations have been investigated, the ingredients of the various materials used in these occupations have been enumerated, and the probability of their being hazards is discussed. This volume is essentially a Bible for those who are interested in industrial diseases. The principal fault to be found is that many of the photographs are poor and might well have been omitted. This book should be useful to all those who are interested in the workmen's compensation laws, especially industrial dermatologists.

H. M. R.

## BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Whooping Cough.* By JOSEPH H. LAPIN, B. Chem., M.D. 238 pages; 23.5 × 15 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $4.50.

*Managing Your Mind.* By S. H. KRAINES, M.D., and E. S. THETFORD. 374 pages; 22 × 15 cm. 1943. The Macmillan Company, New York City. Price, $2.75.

*Nutritional Deficiency in Nervous and Mental Disease.* Volume XXII of Research Publications of the Association for Research in Nervous and Mental Disease. Editorial Board: STANLEY COBB, M.D. (Chairman), EDWIN F. GILDEA, M.D., and HARRY M. ZIMMERMAN, M.D. 215 pages; 23.5 × 15.5 cm. 1943. The Williams & Wilkins Company, Baltimore. Price, $4.00.

*Human Gastric Function.* By STEWART WOLF, M.D., Captain, M.C., A. U. S., and HAROLD G. WOLFF, M.D. With a foreword by WALTER B. CANNON, M.D. 195 pages; 24 × 16 cm. 1943. Oxford University Press, New York City. Price, $4.75.

*Pain Mechanisms.* By W. K. LIVINGSTON, Lieutenant Commander, M.C., U.S.N.R. 253 pages; 22 × 15 cm. 1943. The Macmillan Company, New York City. Price, $3.75.

*Diagnosis of Uterine Cancer by the Vaginal Smear.* By GEORGE N. PAPANICOLAOU, M.D., and HERBERT F. TRAUT, M.D. 73 pages; 28.5 × 21 cm. 1943. The Commonwealth Fund, New York City. Price, $5.00.

# COLLEGE NEWS NOTES

### Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,439 Fellows and Associates of the College on active military duty. Herewith are reported the names of 14 additional members, bringing the grand total to 1,453.

Sidney Adler
Walter S. Burrage
F. Benjamin Carr
John T. Eads
Clarence K. Elliott
Thomas B. Magath
Cornelius C. Perrine
Norman Plummer
David E. Quinn
William F. Rexer
Bernard M. Scholder
Frank E. Smith, Jr.
Solomon C. Werch
I. Sidney Zaur

Captain Milton M. Portis, Medical Corps, California State Guard, has been retired to inactive duty.

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### Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

*Books*

Dr. James B. Herrick, M.A.C.P., Chicago, Ill.—"A Short History of Cardiology."

*Reprints*

Edward L. Bortz, F.A.C.P., Commander, (MC), U. S. Naval Reserve—8 reprints;
George R. Callender, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Dr. Pedro Leandro Farinas Mayo, F.A.C.P., Havana, Cuba—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Isidore W. Held, F.A.C.P., New York, N. Y.—3 reprints;
Walter S. Jensen, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Henry J. John, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—4 reprints;
Dr. Charles E. Lyght, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Berthold S. Pollak, F.A.C.P., Jersey City, N. J.—1 reprint;
Dr. Adolph Sachs, F.A.C.P., Omaha, Nebr.—16 reprints;
Dr. Charles H. Sprague, F.A.C.P., Bridgeport, Conn.—1 reprint;
Dr. J. Manuel Viamonte, F.A.C.P., Havana, Cuba—1 reprint.

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### Dr. Elliott P. Joslin Awarded Distinguished Service Medal of the American Medical Association

Dr. Elliott P. Joslin, F.A.C.P., Boston, was the recipient of the Distinguished Service Medal Award of the American Medical Association for 1943 in recognition of his contribution to our knowledge of diabetes and as an educator in that field. Dr. Joslin is Honorary President of the American Diabetes Association. In 1932 he was the recipient of the Kober Medal of the Association of American Physicians. He has travelled throughout the nation extending instruction on diabetes to the medical pro-

fession and to the public. He has delivered various important lectures, such as the Harvey Society Lecture in Boston, the Stephen Walter Ranson Lecture of Northwestern University Medical School, and the Malthe Lectures.

Other recipients of the Distinguished Service Medal of the American Medical Association have included Dr. Rudolph Matas (1938), Dr. James B. Herrick, M.A.C.P., (1939), Dr. Chevalier Jackson (1940), Dr. James Ewing (1941), and Dr. Ludvig Hektoen (1942).

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Dr. T. Grier Miller, F.A.C.P., Philadelphia, Professor of Clinical Medicine at the University of Pennsylvania School of Medicine, was recently honored by his Alma Mater, the University of North Carolina, by having bestowed upon him the honorary degree of Doctor of Laws.

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Dr. Charles L. Brown, F.A.C.P., Professor of Medicine at Temple University School of Medicine, Philadelphia, was recently appointed by the American Society for Clinical Investigation as a member of that society's committee serving on the National Research Council.

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Dr. Samuel E. Munson, F.A.C.P., Springfield, Ill., was honored at a dinner on June 10, 1943, marking his fifty years in the practice of medicine. The Sangamon County Medical Society Bulletin states that this is a distinction to which only 290 doctors out of 12,500 in Illinois have become eligible.

Dr. Munson was born August 25, 1866, attended Valparaiso University and graduated in medicine from Northwestern University Medical School in 1893. He did postgraduate work at the University of Göttingen in Germany and at the University of Vienna. He has been in practice in Springfield, Ill., since 1899. He has been a Fellow of the American College of Physicians for many years, was one of the original members of its Board of Governors and served as a Vice President in 1941–42. He is a Diplomate of the American Board of Internal Medicine. He has served as President of the Illinois State Medical Society, as President of the Central District Medical Society, as President of the Sangamon County Medical Society, and he was for many years District Councillor of the Illinois State Medical Society.

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Dr. Josiah J. Moore, F.A.C.P., Chicago, Ill., has been elected Treasurer of the American Medical Association to succeed Dr. Herman L. Kretschmer, who was made President-Elect at the Annual Meeting of the House of Delegates in June.

Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill., was reëlected a Trustee of the American Medical Association for a term of five years.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, addressed a meeting of the Tenth and Eleventh Councillor Districts of the Medical Society of the State of Pennsylvania in Washington, Pa., June 17, 1943. Dr. Kelly spoke on "The Concept of Nutrition and Its Application Under War Rationing."

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The New York Academy of Medicine will conduct its 16th Graduate Fortnight, October 11–22, 1943. The subject of this meeting will be "Disorders of the Digestive Tract." Among the speakers who will present papers at the scientific sessions are:

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.—The Ludwig Kast Lecture, "The Physiology of the Gastrointestinal Tract";

Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn.—"Present Status of Regional Enteritis and Ulcerative Colitis";

Thomas T. Mackie, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—"Amebiasis and the Flagellate Diarrheas";
Dr. W. Osler Abbott, F.A.C.P., Philadelphia, Pa.—"The Management of Acute Intestinal Obstruction."

Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., will be Chairman of a panel discussion on "Emotions and Gastric Function" and Dr. Walter A. Bastedo, F.A.C.P., New York, N. Y., Chairman of a panel discussion on "Use of Sulfonamides in Gastro-intestinal Diseases."

Dr. Arthur F. Chace, F.A.C.P., is President and Dr. Mahlon Ashford, F.A.C.P., Secretary of the New York Academy of Medicine. Dr. Bernard S. Oppenheimer, F.A.C.P., is Chairman of the Committee on Medical Education of the Academy that will arrange the program and Dr. F. Warner Bishop, F.A.C.P., is Chairman of the Graduate Fortnight Committee.

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The Kansas City Southwest Clinical Society will hold its 21st Annual Fall Clinical Conference, October 4–6, 1943. Among the guest speakers who will present papers at this conference are:

Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, Pa.;
Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn.;
Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.;
Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.;
Dr. Paul D. White, F.A.C.P., Boston, Mass.

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The Mississippi Valley Medical Society will hold its 9th annual meeting in Quincy, Ill., September 29–30, 1943. Among the well-known clinicians who have accepted places on the program are:

Henry L. Dollard, F.A.C.P., Captain, (MC), U. S. Navy;
Dr. Willis M. Fowler, F.A.C.P., Iowa City, Iowa;
Dr. Samuel F. Haines, F.A.C.P., Rochester, Minn.;
Dr. Archibald L. Hoyne, F.A.C.P., Chicago, Ill.;
Dr. Robert W. Keeton, F.A.C.P., Chicago, Ill.;
Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.

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Dr. Louis Hamman, F.A.C.P., Baltimore, Md., presented the Mellon Lecture sponsored annually by the Society for Biological Research of the School of Medicine of the University of Pittsburgh on May 27, 1943. Dr. Hamman spoke on "Acute Diffuse Interstitial Fibrosis of the Lungs."

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Dr. Burrell O. Raulston, F.A.C.P., has been appointed Dean and Professor of Bacteriology at the University of Southern California School of Medicine in Los Angeles to succeed Dr. Seeley G. Mudd, F.A.C.P., who has resigned. Dr. Raulston has been Professor and Head of the Department of Medicine and Director of Clinical Teaching at the University since 1930.

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Dr. Robert S. Berghoff, F.A.C.P., Chicago, Ill., was recently elected one of the Vice Presidents of the Illinois State Medical Society.

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Dr. Floyd L. Rogers, F.A.C.P., Lincoln, Nebr., has been named President-Elect of the Nebraska State Medical Association.

Dr. Peter Irving, F.A.C.P., New York, N. Y., Secretary of the Medical Society of the State of New York, has been named a member of the Moreland Act Commission by Governor Dewey. This commission will formulate a long range program for the improvement of the mental hygiene hospitals of the State of New York.

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Dr. William H. Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Bethesda, Md., has been named Treasurer of the American Institute of Nutrition.

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Dr. Neuton S. Stern, F.A.C.P., Memphis, Tenn., spoke on "Heart Neurosis" at the 81st semiannual meeting of the First Councilor District Medical Society of Northeast Arkansas at Jonesboro, May 27, 1943.

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Dr. Newton G. Evans, F.A.C.P., Professor and Head of the Department of Pathology and a member of the Board of Trustees of the College of Medical Evangelists, Los Angeles, Calif., was unanimously elected Dean of the College, May 5, 1943.

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Zolton T. Wirtschafter (Associate), Major, (MRC), U. S. Army, spoke on "The Importance of Minerals in Human Nutrition" at the 2nd Annual Conference on Conservation, Nutrition and Human Health held in Tar Hollow, Ohio, June 26–27, 1943.

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The Aero Medical Association of the United States recently elected its first group of twenty-five Fellows in Aviation Medicine. Among the members of the College who were named Fellows of the Association are:

Harry G. Armstrong, F.A.C.P., Colonel, (MC), U. S. Army;
Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y.;
Otis O. Benson, Jr. (Associate), Colonel, (MC), U. S. Army;
Leon D. Carson (Associate), Commander, (MC), U. S. Navy;
John R. Poppen, F.A.C.P., Captain, (MC), U. S. Navy;
Eugen G. Reinartz, F.A.C.P., Brigadier General, (MC), U. S. Army.

The new constitution and by-laws of the Aero Medical Association of the United States provide for the nomination of an initial group of ten Fellows and for the election of fifteen additional Fellows which shall comprise the first group. The by-laws further provide that all subsequent elections to Fellowship shall be made by the Group of Fellows and shall be by selection only from those who have made outstanding contributions to aviation medicine, and that not more than ten shall be elected to Fellowship during any one year.

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On April 5, 1943, Dr. Marcos Fernan-Nunez, F.A.C.P., Milwaukee, Wis., spoke on "War Problems in Tropical Diseases" before the combined medical staffs of Army General Hospital No. 17 and the Post General Hospital of Camp McCoy, Wis.

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Dr. Andrew C. Ivy, F.A.C.P., Dr. Italo F. Volini, F.A.C.P., Dr. Aaron Arkin, F.A.C.P. and Dr. Frederick Steigmann (Associate), all of Chicago, have been named members of the Board of Trustees of the Hektoen Institute for Medical Research of Cook County (Ill.).

Under the Presidency of Dr. Ernest D. Hitchcock, F.A.C.P., Great Falls, the Medical Association of Montana held its 65th Annual Session in Billings, July 7–8 1943. Among the speakers were:

Dr. Wayne Gordon, F.A.C.P., Billings—"Gastritis: Diagnosis and Clinical Significance";
Alexander P. Ormond, F.A.C.P., Major, (MRC), U. S. Army—"The Wartime Spread of Communicable Diseases."

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The Philadelphia Chapter of the National Foundation for Infantile Paralysis is sponsoring a series of eight lectures for physicians, nurses and physical therapists. One of these lectures will be presented by Dr. Pascal F. Lucchesi (Associate), Philadelphia. Dr. Lucchesi will speak on "Diagnostic Signs."

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Under the direction of Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill., the 11th Chicago Institute for Hospital Administrators will be held August 30–September 10, 1943.

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On May 14, 1943, Dr. C. Sidney Burwell, F.A.C.P., Dean of the Harvard Medical School, Boston, Mass., delivered the 6th Annual Gerrish Library Lecture at the Central Main General Hospital, Lewiston, Maine. Dr. Burwell spoke on "Changing Viewpoints as to Disorders of Circulation."

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Dr. William H. Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Bethesda Md., delivered the Marcus A. Rothschild Lecture at Beth Israel Hospital, New York, N. Y., June 15, 1943. Dr. Sebrell spoke on "Trend of Recent Research in Vitamins and Clinical Symptoms of Vitamin Deficiency."

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Dr. Lyell C. Kinney, F.A.C.P., San Diego, Calif., was elected a Vice President of the American College of Radiology at its annual meeting in Chicago, Ill., June 6, 1943.

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The Vancouver Medical Association conducted its summer school in Vancouver, B. C., June 22–25, 1943. Among the speakers were:

Jonathan C. Meakins, F.A.C.P., Brigadier, Royal Canadian Army Medical Corps —"Effort Syndrome and Allied Conditions in Civil and Military Practice";
Dr. Maxwell M. Cantor, F.A.C.P., Edmonton, Alta.—"The Clinical Application of Research in Nutrition."

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Dr. Wm. deB. MacNider, F.A.C.P., Chapel Hill, N. C., Kenan Research Professor of Pharmacology and Head of the Department of Pharmacology of the University of North Carolina School of Medicine, has relinquished the Headship of this Department, to become effective September 1, 1943. He will continue in the Department as a research professor.

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Dr. Chester M. Kurtz, F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School and Dr. N. C. Gilbert, Professor of Medicine, Northwestern University Medical School, were the special guest speakers at a meeting of the Rock County (Wisconsin) Medical Society at Janesville, June 22. The subject was

"Rheumatic Heart Disease and Coronary Heart Disease," with special emphasis on ne convalescent care of cardiac cases.

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The National Foundation for Infantile Paralysis announced, on July 2, twenty-ight grants, totaling $354,370.00, to universities, hospitals, laboratories and other nstitutions in eleven States to continue investigative work in this disease. The funds .re raised annually in January through the celebration of President Roosevelt's birthday.

Sixteen grants, totaling $216,020.00, were made for virus and after-effects research. Four of these are long-term projects being conducted at Yale University, Johns Hopkins University, the University of Michigan and the University of Wisconsin.

Twelve grants, totaling $138,350.00, were made for various educational programs, including the training of technicians in the Kenny method of treatment. Some of these grants include projects for educational work for physicians and the public. $2,500.00 was appropriated for the preparation of a complete bibliography on poliomyelitis.

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Dr. A. B. Brower, F.A.C.P., Dayton, College Governor for Ohio, will be the official representative of the American College of Physicians at the celebration of the one hundredth anniversary of Western Reserve University School of Medicine, to be held at Cleveland, October 27, 1943.

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Dr. Walter Clarke, F.A.C.P., Executive Director of the American Social Hygiene Association, New York City, has been appointed Clinical Professor of Public Health Practice at Harvard University. During the past three years, he has served as Lecturer on Public Health Administrative Practice, as applied to the control of syphilis and gonorrhea, giving ten lectures on this subject each year at the Harvard School of Public Health. In the academic year 1943–44, he will give forty hours of instruction covering the course, diagnosis and treatment of syphilis, gonorrhea, lymphogranuloma venereum, granuloma inguinale and chancroid and the epidemiologic and administration measures for the control of these infections. He will also supervise the field training of the students of public health specializing in venereal disease control.

Dr. Clarke will continue as the Executive Director of the American Social Hygiene Association.

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## SPECIAL NOTICES

### Medical Officers Needed for Federal Civilian War Service

The critical shortage of physicians to engage in vital war work in the civilian branches of the Government continues. The great need for these men resulted in the announcing of a liberalized civil-service examination for Medical Officers in 1941. The Civil Service Commission has just revised and re-announced this examination.

The twenty optional branches under which doctors may apply range from General Practice to Aviation Medicine. Those appointed will perform professional duties as doctors of medicine in active practice in hospitals, in dispensaries, or in the field or in rural areas; or in bureaus of the Government such as the Veterans Administration, Civil Aeronautics Administration, Public Health Service, and Food and Drug Administration. Doctors will also be used in industrial establishments under direction of the War Department.

Applicants for all grades must have received the degree of M.D from an accredited medical school. Applicants for the Senior Medical Officer grade ($5,228

a year) must have had at least 5 years of appropriate medical experience; for the Medical Officer grade ($4,428 a year), 3 years of experience in addition to a required interneship; and for the Associate Medical Officer grade ($3,828), 1 year of interneship. The salaries quoted include overtime pay.

There are no written tests and no age limits. Persons now using their highest skills in war work should not apply for these positions. Appointments in Federal positions are made in accordance with War Manpower policies and employment stabilization plans. Before a definite offer of appointment is made, eligibles are cleared through the Procurement and Assignment Service for Physicians, Dentists, and Veterinarians, of the War Manpower Commission.

Persons rated eligible on the Medical Officer examination of 1941 need not file applications again unless they consider that they now possess qualifications for eligibility in a higher grade or different option.

Further information and application forms may be obtained at first- and second-class post offices, Civil Service Regional Offices, and the Commission in Washington, D. C.

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Fort Des Moines, Iowa, June 19.—Marking a milestone in the recognition of women in medicine, an official ceremony was conducted this morning at First WAAC Training Center, Fort Des Moines, Ia. Dr. Eleanor Gutman and Dr. Elizabeth Garber became Officers in the Medical Corps of the Army of the United States, Dr. Gutman as a Captain and Dr. Garber as a First Lieutenant. They are the second and third ranking women in the Corps, Maj. Margaret Craighill being the first ranking.

Serving with the Women's Army Auxiliary Corps at First WAAC Training Center, first in the capacity of contract surgeons and then as Women's Army Auxiliary Corps Officers, the women physicians have been associated closely with the WAAC almost since its beginning.

The official ceremony took place in the Post Headquarters office with Maj. E. R. Payne, Post Adjutant, administering the oath of office.

Both Officers have had the rank of Second Officer which is the WAAC rank equivalent to First Lieutenant in the Army.

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A Chinese blood bank, opened June 7 at 154 Nassau Street, New York City, to seek blood donations for soldiers of the Chinese armies, will accept the blood of persons who have had malaria, according to its sponsor, the American Bureau for Medical Aid to China. This can be done by using the Seitz filter, which eliminates malaria microörganisms.

Almost every Chinese has had malaria at some time in his life, and the sponsors of the project realized that there could be few Chinese donors to the blood bank if persons who had suffered from the disease were ruled out. Dr. John Scudder of Presbyterian Hospital, who as Chairman of the Blood Bank Committee of ABMAC has been largely responsible for carrying through the project, had tested and proved the efficacy of the filter in Puerto Rico.

Blood donations received at the bank are converted in its own laboratories into dry plasma and shipped to China in American army planes. The medical staff members of the blood bank, all of whom are Chinese, have had special training in American hospitals for this work and eventually will go to China as a unit to set up the first blood bank there.

## *OBITUARIES*

### DR. ARTHUR CONKLIN BRUSH

Dr. Arthur Conklin Brush, F.A.C.P., New York, N. Y., died on March 17, 1943, in the Methodist Hospital in Brooklyn of broncho-pneumonia, at the age of eighty years.

Dr. Brush was born in Brooklyn in 1862, attended the Polytechnic Institute, received the Degree of Doctor of Medicine from Columbia University College of Physicians and Surgeons in 1884. For many years he was a Visiting Neurologist and Consultant in the Kings County Hospital, Brooklyn Eye and Ear Hospital, Coney Island Hospital, and House of St. Giles the Crippled.

He had been retired from active practice for a number of years although he continued some medico-legal work for some years after his retirement. He was the author of numerous papers, was an Affiliate Fellow of the American Medical Association; Member of the Kings County Medical Society, Medical Society of the State of New York, New York Neurological Society, Brooklyn Pathological Society, Society of Medical Jurisprudence, and a Fellow of the American College of Physicians since 1920.

Dr. Brush was one of the last of the Old School, a highly respected citizen of the community, and his passing is a distinct loss to the medical profession and to his friends.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

### DR. HUGH ATLEE BEAM

Dr. Hugh Atlee Beam, F.A.C.P., Moline, Ill., was born July 15, 1882, at Dakota City, Iowa. He graduated from Northwestern University Medical School in 1903. Thereafter he practiced medicine in Iowa for three years and then removed to Moline, Ill., where he developed an extensive practice, which he kept up until the time of his death.

Dr. Beam did graduate work at Glen Lake Sanitorium, near Minneapolis. He was a past President of the Rock Island County (Ill.) Medical Society and of the Iowa State Medical Society, and a member of the State Medical Legislative Committee and of the Trudeau Society. For eight years he was Medical Director of the Rock Island County Tuberculosis Sanitorium.

Dr. Beam died March 30, 1943, following an operation on the cervical spine at St. Luke's Hospital, St. Louis, aged sixty. He was a most highly respected physician and counsellor to the sick and to people in distress. Thousands of people in this community will mourn his passing.

WILLIAM F. SCHROEDER, M.D., F.A.C.P.,
Rock Island, Ill.

## DR. FRANK R. BORDEN

Lt. Col. Frank R. Borden, (MC), U. S. A. (Retired), Fellow of the American College of Physicians, died in the Veterans Administration Facility at Augusta, Ga., March 28, 1942, of pneumonia, aged 68 years.

Colonel Borden was born in Wisconsin, November 1, 1874. He studied Pharmacy at Northwestern University, graduating in 1896, Ph.G. He received his medical degree in 1902 from the University of Illinois College of Medicine. Thereafter he served as Health Officer at Plainfield, Wis., and as local Surgeon to the Minneapolis, St. Paul and S. St. Marie Railroad. He served one year, 1907, as Instructor in Pharmacology at the College of Physicians and Surgeons of Milwaukee. On June 13, 1917, he entered the Medical Reserve Corps of the U. S. Army as First Lieutenant, serving during World War I, and remaining in the Corps after the War. He did post-graduate study at the University of Dijon (France) in 1919, and in 1924 graduated as a Flight Surgeon from the School of Aviation Medicine of the U. S. Army. For several years he served as Assistant Commandant and Director of the Extension Course of the School of Aviation Medicine. In 1937 he was retired from active duty, because of physical disability. He maintained Fellowship in the American Medical Association, and had been a Fellow of the American College of Physicians since 1936.

## DR. WILLIAM HARRIS FUNK

Dr. William Harris Funk, F.A.C.P., Captain, (MC), U. S. Navy, died January 7, 1943, following twenty-two years in Naval Service.

Captain Funk was born at South Bend, Ind., May 14, 1893; received his A.B. degree from Williams College in 1916 and his M.D. degree from Johns Hopkins University School of Medicine in 1920. He immediately entered the Medical Corps of the Navy, and thereafter served on many assignments in various parts of the world where the Navy maintains its stations. In the course of his career he did postgraduate work not only at the U. S. Naval Medical School at Washington, D. C., but at the University of Pennsylvania Graduate School of Medicine in Philadelphia and the Massachusetts General Hospital in Boston.

He was a Diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

## DR. CHARLES F. GORMLY

Dr. Charles Francis Gormly died June 26, 1943, at Providence.

A native of Providence, where he practiced internal medicine for thirty-two years, Dr. Gormly has brought to a close one of the most valuable medi-

cal careers in the history of Rhode Island. He was graduated from Tufts Medical School in 1909 and spent three years on the neurological and medical services at the Boston City Hospital. During the first World War he served with the British Army and later in the Army of the United States in which he held the rank of Major and was Physician-in-Chief of the 13th Evacuation Hospital in France. It was he who did practically all the ground work in the organization of the 68th Evacuation Hospital which was recruited from the staff of the Rhode Island Hospital and is now serving in India.

After many years as Visiting Physician Dr. Gormly four years ago became Physician-in-Chief of the Medical Service at the Rhode Island Hospital. Just before his death he completed a most successful year as President of the State Medical Society—a year which he brought to completion by an exhibition of sheer pluck that will be long remembered by his colleagues.

A number of signal honors came to him in his last few years. He was always a most enthusiastic member of our College and a regular attendant at its sessions. Many will remember him as the genial Chairman and Toastmaster at the first New England Regional Meeting of the College when, it was later discovered, he was already beginning to suffer from the condition of which he died about a year and a half later.

After thirty-three years of intimate friendship and association with Dr. Gormly the writer finds it impossible adequately to express his thoughts and feelings but will quote from his own contribution to the Rhode Island Medical Journal. "The value of his life to his friends and colleagues, to his casual acquaintances, indeed to every citizen of Rhode Island, is beyond our ability to estimate.

"Throughout the thirty-one years of his active practice he has always been a dynamic force for the betterment of the condition of his patients, his medical associates, his hospital and his community. Up to the time of his death he preserved a cheerful optimism and a clear-sighted interest in the planning of a future in which he know he could not share.

"Always, even in the face of inevitable physical suffering and disaster his ready wit and glowing humor never failed. For almost a year and a half, as was generally known, he suffered the progressive inroads of an incurable malady and yet he carried on undaunted as practitioner, consultant and physician-in-chief and in addition brought to a most successful conclusion his year as President of the Rhode Island Medical Society.

"The courage with which he fought this campaign through equals the most heroic deeds for which men are decorated on the field of battle. He is a life-long inspiration to us all."

ALEX. M. BURGESS,
Governor for Rhode Island

## DR. ROY MUNRO COLLIE

Dr. Roy Munro Collie (Associate), Schenectady, N. Y., died April 24, 1943, of hypertensive heart disease, at the age of 59 years.

Dr. Collie was born at Gloversville, N. Y., graduated from the Albany Medical College in 1906, and for a great many years was connected in various capacities with the Ellis Hospital at Schenectady. His was a life time of service in that community. He was a member of the Schenectady Academy of Medicine, the New York State Medical Society, the Schenectady County Medical Society, and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since 1926, having first become a member of the former American Congress on Internal Medicine in 1920. When that organization was merged with the College, he automatically was made an Associate and maintained that membership to the time of his death.

# POSTGRADUATE COURSES BY THE AMERICAN COLLEGE OF PHYSICIANS, AUTUMN, 1943

The following courses have been arranged through the generous coöperation of the Directors and the institutions at which the courses will be given. The Advisory Committee on Postgraduate Courses will plan other courses during the winter and spring of 1944. These courses are organized especially for Fellows and Associates of the College, but where facilities are available, courses will be open to those with adequate preliminary training, including Medical Officers of the Armed Forces, who are now preparing either to meet the requirements for membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College assumes the expenses of promotion, advertising, printing and registration. Physicians on active duty in the Armed Forces will be granted free tuition.

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## COURSE NO. 1—ENDOCRINOLOGY

(October 11–16, 1943)

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE AND THE PRESBYTERIAN HOSPITAL

1753 W. Congress St., Chicago, Ill.

WILLARD O. THOMPSON, M.D., F.A.C.P., *Director*

Fee, $20.00

### OFFICERS OF INSTRUCTION

Fuller Albright, M.D., Associate Professor of Medicine, Harvard Medical School, Boston, Mass.

Percival Bailey, M.D., Professor of Neurosurgery, University of Illinois College of Medicine.

Anton J. Carlson, M.D., F.A.C.P., Professor of Physiology, Emeritus, University of Chicago, The School of Medicine.

Lester R. Dragstedt, M.D., Professor of Surgery, University of Chicago, The School of Medicine.

Carl Hartman, Ph.D., Professor and Head of the Department of Zoology and Physiology, University of Illinois.

Norris J. Heckel, M.D., F.A.C.S., Assistant Professor of Urology, University of Illinois College of Medicine.

Charles R. Huggins, M.D., Professor of Surgery (Genito-Urinary), University of Chicago, The School of Medicine.

Andrew C. Ivy, M.D., F.A.C.P., Professor of Physiology, Northwestern University Medical School.

Robert W. Keeton, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Illinois College of Medicine.

A. T. Kenyon, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.

F. C. Koch, Ph.D., Professor of Biochemistry, Emeritus, University of Chicago.

Carl R. Moore, Ph.D., Professor and Head of the Department of Zoology, University of Chicago.

J. deJ. Pemberton, M.D., F.A.C.S., Professor of Surgery, University of Minnesota Medical School; Head of Section in Surgery, Mayo Clinic; Rochester, Minn.
Edward H. Rynearson, M.D., F.A.C.P., Assistant Professor of Medicine, University of Minnesota Medical School; Consultant in Medicine, Mayo Clinic; Rochester, Minn.
Elmer L. Sevringhaus, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.
David Slight, M.D., Professor of Psychiatry, University of Chicago, The School of Medicine.
Willard O. Thompson, M.D., F.A.C.P., Associate Professor of Medicine, University of Illinois College of Medicine.
Rollin T. Woodyatt, M.D., Professor of Medicine, University of Illinois College of Medicine.

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Wherever possible in this course in Endocrinology, all clinical discussions will be illustrated by the demonstration of patients.

In the preclinical sciences, discussion will be amplified by the presentation of actual specimens, by lantern slides and by microscopic demonstration.

All meetings will be held in one of the amphitheaters in the Presbyterian Hospital (1753 W. Congress St.). Arrangements will be made for luncheons at the Illini Union (715 S. Wood St.).

All those desiring to take the course are urged to make their hotel reservations early, because of the great demand for accommodations.

### Outline of Course

Monday, October 11.

Some Significant Milestones in Our Understanding of the Endocrines.
Dr. Carlson.
Endocrine Clinic: Diseases of the Thyroid.
Dr. Thompson.
Ketosis and Diabetes: Present Status of the Problem.
Dr. Woodyatt.
Principles Involved in the Treatment of Diabetes Mellitus.
Dr. Keeton.

Tuesday, October 12.

Endocrine Treatment of Cancer of the Prostate.
Dr. Huggins.
Endocrine Clinic: Hypogonadism.
Dr. Thompson.
Influence of Sex Hormones on Spermatogenesis; Technique of Spermatozoa Counts; Evaluation of Sex Hormones in the Treatment of Obstruction at the Neck of the Bladder.
Dr. Heckel.
Hormone Assays in Blood and Urine: Clinical Significance and Practical Application.
Dr. Koch.
Pineal Disorders; Surgery of the Pituitary.
Dr. Bailey.
Lipocaic and Fat Metabolism.
Dr. Dragstedt.

Wednesday, October 13.

Dwarfism and Primary Ovarian Deficiency.
Dr. Kenyon.
Endocrine Disturbances Related to Deformations of the Genital Apparatus.
Dr. Ivy.
Endocrine Regulation of Menstruation: Clinical Significance.
Dr. Hartman.
Endocrine Clinic: Hypogonadism (Continued).
Dr. Thompson.

Thursday, October 14.

The Development of the Ovary and Testis: Clinical Application.
Dr. Moore.
Endocrine Clinic: Diseases of the Adrenals, with Special Reference to Addison's Disease.
Dr. Thompson.
Diseases of the Parathyroids.
Dr. Albright.
Psychotic Episodes in Endocrine Disorders.
Dr. Slight.

Friday, October 15.

Endocrine Clinic: Pituitary Disorders.
Dr. Thompson.
Some New Clinical Syndromes.
Dr. Albright.
Diseases of the Pituitary.
Dr. Rynearson.
Carcinoma of the Thyroid.
Dr. Pemberton.
Endocrine Disturbances of the Female Reproductive System.
Dr. Sevringhaus.

Saturday, October 16.

This day will be devoted to the Regional Meeting of the American College of Physicians at the Drake Hotel, Chicago, representing the States of Wisconsin, Iowa, Illinois, Indiana and Michigan. Detailed program later.

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## COURSE NO. 2—ALLERGY

(October 25–30, 1943)

ROOSEVELT HOSPITAL, NEW YORK, N. Y.

ROBERT A. COOKE, M.D., F.A.C.P., *Director*

(Minimal Registration, 25; Maximal Registration, 50)

Fee, $20.00

### OFFICERS OF INSTRUCTION

Robert A. Cooke, M.D., F.A.C.P., Attending Physician and Director, Department of Allergy, Roosevelt Hospital.

Horace S. Baldwin, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician and Chief of the Allergy Clinic, New York Hospital.

Aaron Brown, M.D., Assistant Clinical Professor of Medicine and Chief of Allergy Clinic, New York University College of Medicine; Assistant Visiting Physician, Bellevue Hospital.

Robert Chobot, M.D., F.A.C.P., Assistant Professor of Clinical Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Pediatric Allergy, New York Post-Graduate Medical School and Hospital; Assistant Chief, Allergy Clinic, Roosevelt Hospital.

Russell Clark Grove, M.D., Associate Surgeon, Otolaryngology, Roosevelt Hospital.

Joseph Harkavy, M.D., Associate in Medicine, Columbia University College of Physicians and Surgeons; Associate Physician and Chief of Allergy Clinic, Mt. Sinai Hospital; Associate Physician, Montefiore Hospital.

Selian Hebald, M.D., Assistant Chief of Allergy Clinic, Roosevelt Hospital; Senior Clinical Assistant in Allergy, Outpatient Department, Mt. Sinai Hospital.

Michael Heidelberger, Ph.D., Associate Professor of Biochemistry, Columbia University College of Physicians and Surgeons; Chemist, Presbyterian Hospital.

Beatrice Kesten, M.D., Dermatologist, Presbyterian Hospital and Vanderbilt Clinic; Associate Dermatologist, Welfare Hospital for Chronic Diseases.

Paul Klemperer, M.D., Pathologist, Mt. Sinai Hospital.

Will Cook Spain, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Medical School and Hospital.

Arthur Stull, Ph.D., Captain, U. S. Army Sanitary Corps.

Marion Sulzberger, M.D., Commander, (MC), U.S.N.R.

Albert Vander Veer, M.D., Consultant in Allergy and Chief of Allergy Clinic, Roosevelt Hospital.

Matthew Walzer, M.D., Associate in Medicine, Cornell University Medical College; Attending in Allergy and Chief of Allergy Clinic, Jewish Hospital, Brooklyn.

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To make this course available to a larger group than formerly, it was decided to resort to the more didactic type of presentation with lectures, clinics and conferences. While the course is to be given at the Roosevelt Hospital, the Officers of Instruction have been drawn from many medical schools and hospitals throughout the City. All phases of Allergy—immunological, pathological and clinical—will be covered, including theoretical and practical aspects with the idea of furnishing the internist, the general practitioner or allergist with the latest information. On the last morning (October 30) there will be an optional session devoted to the preparation of allergen extracts and vaccines, and practical experience in testing.

### Outline of Course

Monday, October 25.

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| A.M. | |
| 9:00–11:30 | Registration.<br>Introduction to Allergy.<br>Dr. Cooke. |
| 11:30– 1:00 | Extracts: Methods of Preparation and Standardization.<br>Dr. Spain. |
| P.M. | |
| 2:00– 4:00 | Skin Tests.<br>Dr. Walzer. |
| 4:00– 6:00 | Seasonal Hay Fever (1st session).<br>Dr. Vander Veer. |

Tuesday, October 26.

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|---|---|---|
| A.M. | | |
| 9:00–11:00 | Pediatric Allergy. | Dr. Chobot. |
| 11:00– 1:00 | Vasomotor Rhinitis. | Dr. Brown. |
| P.M. | | |
| 2:00– 4:00 | Seasonal Hay Fever (2nd session). | Dr. Vander Veer. |
| 4:00– 6:00 | Immunology. | Dr. Heidelberger. |

Wednesday, October 27.

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| A.M. | | |
| 9:00–11:00 | Atopic Asthma. | Dr. Spain. |
| 11:00– 1:00 | Pathology. | Dr. Klemperer. |
| P.M. | | |
| 2:00– 4:00 | Sinus Disease in Relation to Allergy. | Dr. Grove. |
| 4:00– 6:00 | Infective Asthma. | Dr. Cooke. |
| 8:30 | Conference. | (All members). |

Thursday, October 28.

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| A.M. | | |
| 9:00–11:00 | Asthma—Differential Diagnosis, Serum, Drug and Insulin Allergy. | Dr. Baldwin. |
| 11:00– 1:00 | Vascular Allergy, Menier's Disease, Migraine, Physical Allergy. | Dr. Harkavy. |
| P.M. | | |
| 2:00– 3:00 | Seasonal Hay Fever—Special Features. | Dr. Hebald. |
| 3:00– 5:00 | Miscellaneous Allergies. | Dr. Cooke. |

Friday, October 29.

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| A.M. | | |
| 9:00–11:00 | Contact Dermatitis. | Dr. Sulzberger. |
| 11:00– 1:00 | Eczema, Urticaria, Angioneurotic Edema. | Dr. Kesten. |
| P.M. | | |
| 2:00– 5:00 | Clinic. | Dr. Cooke. |
| 8:00 | Dinner and Roundtable. | |

Saturday, October 30.

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| A.M. | | |
| 9:00 | Optional—Practical Work on Tests, Extracts, etc. | Dr. Stull, et al. |

## Reading List and Bibliography

### Course No. 2

An attempt is made to obtain reading lists for each Postgraduate Course for publication in the Annals of Internal Medicine, making these lists available to the entire membership of the College, in addition to preparing better the men who will take the courses. These lists are not to be considered as all-inclusive.

*Textbooks*

Practice of Allergy. Warren T. Vaughan. C. V. Mosby Co., St. Louis, 1939.

Asthma and Hay Fever in Theory and Practice. A. F. Coca, M. Walzer and A. A. Thommen. Charles C. Thomas, Baltimore, 1931.

Clinical Allergy. Louis Tuft. W. B. Saunders Co., Philadelphia, 1937.

Occupational Diseases of the Skin. Louis Schwartz and Louis Tulipan. Lea and Febiger, Philadelphia, 1939.

*Monographs*

Allergy. C. E. Von Pirquet. Archives of Internal Medicine *7:* 259, 1911.

Anaphylaxis, Hypersensitiveness and Allergy. W. W. C. Topley. An Outline of Immunity, Chapter 12, p. 192. Wm. Wood Co., 1935.

Hypersensitiveness, Anaphylaxis, Allergy. H. Gideon Wells. The Chemical Aspects of Immunity, Chapter 9, p. 225, second edition. Chemical Catalog Co., New York, 1929.

Diseases of Allergy. Robert A. Cooke. Chapter 21, p. 1079, Internal Medicine. John H. Musser. Lea and Febiger, Philadelphia, 1938, third edition.

Diseases of Allergy. Robert A. Cooke. Page 535, A Textbook of Medicine. Russell L. Cecil. W. B. Saunders Co., Philadelphia, 1940, fifth edition.

Human Sensitization. Robert A. Cooke and A. Vander Veer. Journal of Immunology *1:* 201, 1916.

Herter Lectures. H. H. Dale. Bulletin Johns Hopkins Hospital *31:* pps. 257, 310, 373, 1920.

Anaphylaxis. Carl A. Dragstedt. Physiol. Rev. *21:* 563, 1941.

Histamine and Anaphylaxis. W. Feldberg. Annual Review of Physiology, March 1941.

*Articles*

*Immunological Basis of Sensitization*

Horse Asthma Following Blood Transfusion. M. A. Ramirez. J. A. M. A. *73:* 984, 1919.

Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility. Arent de Besche. Am. J. Med. Sciences *166:* 265, 1923.

Indirect Method of Testing. M. Walzer. J. Allergy *1:* 231, 1930.

Studies in Hypersensitiveness. XXXVI. A Comparative Study of Antibodies Occurring in Anaphylaxis, Serum Disease and the Naturally Sensitive Man. Robert A. Cooke and W. C. Spain. J. Immunol. *17:* 295, 1929.

Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals. W. B. Sherman, A. Stull and S. F. Hampton. J. Immunol. *36:* 447, 1939.

Serological Evidence of Immunity with Co-existing Sensitization in a Type of Human Allergy. Hay Fever. R. A. Cooke, J. H. Barnard, S. Hebald and A. Stull. J. Exper. Med. *62:* 773, 1935.

Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients. M. H. Loveless. J. Immunol. *38:* 25, 1940.

Studies in the Transmission of Sensitization from Mother to Child in Human Beings. S. D. Bell and Z. Eriksson. J. Immunol. *20:* 447, 1931.

The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke. J. Exper. Med. *72:* 611, 1940.

The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk. H. H. Donnally. J. Immunol. *19:* 15, 1930.

The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin. E. L. Burky. J. Allergy *5:* 466, 1934.

*General Clinical Allergy*

History Taking in Allergic Diseases. F. M. Rackemann. J. A. M. A. *106:* 976, 1936.

Studies in Specific Hypersensitiveness. III. On Constitutional Reactions: The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injection of Allergens. R. A. Cooke. J. Immunol. *7:* 119, 1922.

The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. F. F. Furstenberg and L. N. Gay. Bull. Johns Hopkins Hospital *60:* 412, 1937.

The Delayed Type of Allergic Reaction. R. A. Cooke. Ann. Int. Med. *3:* 658, 1930.

Treatment of Allergic Disorders with Histamine and Histaminase. H. L. Alexander. J. Lab. & Clin. Med. *26:* 110, 1940.

*Asthma*

Asthma in Children. R. A. Cooke. J. A. M. A. *102:* 664, 1934.

Infective Asthma. Indication of Its Allergic Nature. R. A. Cooke. Am. J. Med. Sci. *183:* 309, 1932.

Relation of Asthma to Sinusitis with Special Reference to the Results from Surgical Treatment. R. A. Cooke and R. C. Grove. Arch. Int. Med. *56:* 779, 1935.

The Pathology of Bronchial Asthma. H. L. Huber and K. K. Koessler. Arch. Int. Med. *30:* 689, 1922.

Effects on Heart of Long Standing Bronchial Asthma. H. L. Alexander, D. Luten and W. B. Kountz. J. A. M. A. *88:* 882, 1927.

Deaths from Bronchial Asthma. W. B. Kountz and H. L. Alexander. Arch. Path. *5:* 1003, 1928.

Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma. R. A. Cooke. J. Immunol. *7:* 147, 1922.

Asthma Due to a Fungus-Alternaria. J. G. Hopkins, R. W. Denham and B. M. Kesten. J. A. M. A. *94:* 6, 1930.

*Nasal Allergies*

Seasonal Hay Fever and Asthma Due to Molds. S. M. Feinberg. J. A. M. A. *107:* 1861, 1936.

Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps. R. A. Kern. J. A. M. A. *103:* 1293, 1934.

The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever. R. A. Cooke and A. Stull. J. Allergy *4:* 87, 1933.

New Plan for Applying Specific Treatment of Pollen Hay Fever (Perennial Treatment). Aaron Brown. J. Immunol. *13:* 273, 1927.

The Relative Merits of Seasonal and Perennial Treatment of Hay Fever. A. Vander Veer. J. Allergy *7:* 578, 1936.

Calculating Pollen Concentration of the Air. E. C. Cocke. J. Allergy *8:* 601, 1937.

Evaluation of the Ragweed Hay Fever Resort Areas of North America. O. C. Durham. J. Allergy *8:* 175, 1937.

*Intestinal Allergy*

Gastrointestinal Manifestations of Allergy. R. A. Cooke. Bull. N. Y. Acad. Med. Second Series *IX:* 15, 1933.

Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy. W. T. Vaughan. Rev. Gastroenterol. *5:* 1, 1938.

*Skin Allergy*

A Tentative Classification of Allergic Dermatoses. M. B. Sulzberger, F. Wise and J. Wolf. J. A. M. A. *104:* 1489, 1935.

A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years. A. I. Fink and L. N. Gay. J. Allergy *5:* 615, 1934.

Eczema. L. W. Hill. Vol. IV., Chapter 43, Brenneman's Practice of Pediatrics. W. F. Prior Co., Hagerstown, Md.

Studies in Specific Hypersensitiveness. XXVII. Dermatitis Venenata: Toxicodendron Radicans. W. C. Spain and R. A. Cooke. J. Immunol. *13:* 93, 1927.

Report of the Investigation and Successful Treatment (Preventive) of Dermatitis Resulting from the Handling of Tulip Bulbs. A. H. W. Caulfeild. J. Allergy *8:* 181, 1937.

*Miscellaneous Allergy*

Cerebral Symptoms Induced by Angioneurotic Edema. F. Kennedy. Arch. Neurol. and Psychiat. *15:* 28, 1926.

Allergic Migraine. W. T. Vaughan. J. A. M. A. *88:* 1983, 1927.

Food Allergy in Henoch's Purpura. H. L. Alexander and C. H. Eyermann. Arch. Dermat. & Syph. *16:* 332, 1927.

The Clinical Diagnosis of Periarteritis Nodosa. M. B. Cohen, B. S. Kline and A. M. Young. J. A. M. A. *107:* 1555, 1936.

Allergy Induced by Immunization with Tetanus Toxoid. R. A. Cooke, S. F. Hampton, W. B. Sherman and A. Stull. J. A. M. A. *114:* 1854, 1940.

Elimination of Horse Serum Specificity from Antitoxins. R. D. Coghill, N. Fell, M. Creighton and G. Brown. J. Immunol. *39:* 207, 1940.

Physical Allergy. W. W. Duke. J. A. M. A. *84:* 736, 1925.

Allergy in Drug Idiosyncrasy. R. A. Cooke. J. A. M. A. *73:* 759, 1919.

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## COURSE NO. 3—SPECIAL MEDICINE

(November 8–19, 1943)

PHILADELPHIA INSTITUTIONS

CHARLES L. BROWN, M.D., F.A.C.P., *Director*

Fee, $40.00

The Advisory Committee on Postgraduate Courses of the College, in coöperation with authorities in Philadelphia and under the direction of Dr. Charles L. Brown, Professor of Medicine at Temple University School of Medicine, has drawn up an unique program, which should attract the interest of a large number of members of the College, as well as Medical Officers of the Armed Forces. It offers a short, but detailed, resumé in several different specialties. The plan is to allot approximately one-half day to the consideration of each of the special fields of medicine covered in the program. In most instances discussions will be conducted by authorities of national repute.

The concluding day, Friday, November 19, will be devoted to a Regional Meeting of the American College of Physicians for Pennsylvania, New Jersey, Delaware and adjacent territory. The program will consist of a series of clinics in the morning by the staff of the Hospital of the University of Pennsylvania; a luncheon at 1:00 P.M. at the College Headquarters, 4200 Pine Street; and an afternoon program, consisting of six important papers, three by Officers of the Armed Forces and three by outstanding civilian clinicians. In the evening there will be cocktails and dinner at the Benjamin Franklin Hotel, and an interesting program, in which Officers and Regents of the College and high ranking Officers of the Medical Corps of the Armed Forces will participate.

The following outline of the course is in some instances incomplete, or subject to minor changes.

### Officers of Instruction (partial list only)

Edwin B. Abramson, M.D., Assistant, Medical Department, Jewish Hospital.

Kenneth E. Appel, M.D., F.A.C.P., Senior Psychiatrist, Institute of the Pennsylvania Hospital; Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine.

Joseph T. Beardwood, Jr., M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.

Herman Beerman, M.D., Assistant Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, and Assistant Director, Institute for the Control of Syphilis, University of Pennsylvania.

Mary A. Bennett, Ph.D., Physiological Chemist, Lankenau Hospital Research Institute.

Alton D. Blake, M.D., Resident in Pathology, Bryn Mawr Hospital.

Henry L. Bockus, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Earl D. Bond, M.D., Director of Research, Institute of the Pennsylvania Hospital; Professor of Psychiatry and Vice Dean, University of Pennsylvania Graduate School of Medicine.

Robert W. Briggs, Ph.D., Biologist, Lankenau Hospital Research Institute.

Charles L. Brown, M.D., F.A.C.P., Professor of Medicine and Head of the Department of Medicine, Temple University School of Medicine.

W. Edward Chamberlain, M.D., F.A.C.P., Professor of Radiology, Temple University School of Medicine.

F. W. Chornock, M.D., Biochemist, Bryn Mawr Hospital.

Louis H. Clerf, M.D., F.A.C.P., Professor of Laryngology and Bronchoscopy, Jefferson Medical College of Philadelphia.

David A. Cooper, M.D., F.A.C.P., Physician to Division of Tuberculosis, Philadelphia General Hospital; Assistant Professor of Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine.

Gilbert L. Dunnahoo, M.D., Assistant Surgeon General, United States Public Health Service.

John Eiman, M.D., F.A.C.P., Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine; Director of Laboratories, Abington Memorial Hospital.

Gilson C. Engel, M.D., Chief, Surgical Service "B," Lankenau Hospital; Assistant Professor of Surgery, University of Pennsylvania Graduate School of Medicine.

O. Spurgeon English, M.D., Professor of Psychiatry, Temple University School of Medicine.

A. F. Finkelstein, M.D., Associate in Radiology, University of Pennsylvania Graduate School of Medicine.

Harrison F. Flippin, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine.

William I. Gefter, M.D., Clinical Instructor in Medicine, Woman's Medical College of Pennsylvania.

Horace R. Getz, M.D., Associate in Medicine, University of Pennsylvania School of Medicine.

Herbert M. Goddard, M.D., Coroner, City of Philadelphia.

Benjamin A. Gouley, M.D., Chief Coroner's Physician, City of Philadelphia.

George C. Griffith, M.D., F.A.C.P., Assistant Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

Joseph Hughes, M.D., Director of Laboratories, Institute of the Pennsylvania Hospital; Assistant Professor of Experimental Neurology, University of Pennsylvania Graduate School of Medicine.

Norman R. Ingraham, Jr., M.D., Chief, Division of Venereal Disease Control, Philadelphia Department of Public Health; Assistant Professor of Dermatology and Syphilology, School of Medicine, and Associate Director, Institute for the Control of Syphilis, University of Pennsylvania.

Rudolph Jaeger, M.D., Assistant Professor of Neurosurgery, Jefferson Medical College of Philadelphia.

Walter G. Karr, M.D., Assistant Professor of Biological Chemistry, University of Pennsylvania Graduate School of Medicine; Consultant Biochemist, Bryn Mawr Hospital.

Joseph V. Klauder, M.D., Associate Professor of Dermatology and Syphilology, University of Pennsylvania Graduate School of Medicine; Director, Ocular Syphilis Clinic, Wills Hospital.

William Harding Kneedler, M.D., Associate in Tropical Medicine, Jefferson Medical College of Philadelphia.

John A. Kolmer, M.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine; Director, Research Institute of Cutaneous Medicine; Consultant in Serology, U. S. Public Health Service.

Karl Kornblum, M.D., Associate Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

David W. Kramer, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College of Philadelphia.

Paul R. Leberman, Lt., (MC-V-S), U.S.N.R.

W. E. Lee, M.D., F.A.C.S., Vice Dean of Surgery, University of Pennsylvania Graduate School of Medicine.

Rubin M. Lewis, M.D., Acting Chief, Surgical Division, Tuberculosis, Philadelphia General Hospital; Clinical Associate Professor of Surgery, Woman's Medical College of Pennsylvania.

John S. Lockwood, M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania School of Medicine.

Max B. Lurie, M.D., Assistant Professor of Experimental Pathology, University of Pennsylvania Graduate School of Medicine.

C. H. Mann, M.D., Research Institute, E. R. Squibb & Sons, New York, N. Y.

Albert G. Martin, M.D., Surgical Service "A," Lankenau Hospital; Assistant Instructor in Surgery, University of Pennsylvania Graduate School of Medicine.

Hans May, M.D., F.A.C.S., Surgical Service "B," Lankenau Hospital; Associate in Surgical Pathology, University of Pennsylvania Graduate School of Medicine.

Grace Medes, Ph.D., Physiological Chemist, Lankenau Hospital Research Institute.

Merle M. Miller, M.D., F.A.C.P., Associate in Allergy, University of Pennsylvania Graduate School of Medicine; Chief of Allergy Clinic, Graduate Hospital of the University of Pennsylvania.

J. Monaghan, M.D., Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

John R. Moore, M.D., F.A.C.S., Professor of Orthopedics, Temple University School of Medicine.

Julia Morgan, M.D., Professor of Tropical Medicine, University of Pennsylvania School of Medicine.

Harry E. Morton, Sc.D., Associate Professor of Bacteriology, University of Pennsylvania School of Medicine.

Meyer Naide, M.D., Instructor in Medicine, University of Pennsylvania School of Medicine.

H. Ostrum, M.D., Associate Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

Harold D. Palmer, M.D., F.A.C.P., Senior Psychiatrist, Institute of the Pennsylvania Hospital; Professor of Psychiatry, Woman's Medical College of Pennsylvania.

Eugene Pendergrass, M.D., Professor of Radiology, University of Pennsylvania School of Medicine.

Wm. Harvey Perkins, M.D., F.A.C.P., Dean and Professor of Preventive Medicine, Jefferson Medical College of Philadelphia.

Alison H. Price, M.D., Fellow in Medicine, Jefferson Medical College of Philadelphia.

Hobart A. Reimann, M.D., Magee Professor of Practice of Medicine and Clinical Medicine, Jefferson Medical College of Philadelphia.

Stanley P. Reimann, M.D., F.A.C.P., Associate Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine; Pathologist and Director of Research Institute, Lankenau Hospital.

John C. Reinhold, Ph.D., Principal Biochemist, Philadelphia General Hospital.

Jane Royle, M.A., Assistant Biologist, Lankenau Hospital Research Institute.

William G. Sawitz, M.D., Assistant Professor of Parasitology, Jefferson Medical College of Philadelphia.

Michael Scott, M.D., F.A.C.S., Assistant Professor of Neurosurgery, Temple University School of Medicine.

Florence Seibert, M.D., Associate Professor of Biochemistry, University of Pennsylvania School of Medicine.

Thomas A. Shallow, M.D., F.A.C.S., Professor of Surgery, Jefferson Medical College of Philadelphia.

Lauren H. Smith, M.D., F.A.C.P., Physician-in-Chief and Administrator, Institute of the Pennsylvania Hospital; Associate Psychiatrist, University of Pennsylvania School of Medicine.

Will Cook Spain, M.D., F.A.C.P., Professor of Clinical Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Allergy Clinic, New York Post-Graduate Medical School and Hospital; New York, N. Y.

John H. Stokes, M.D., Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, and Director, Institute for the Control of Syphilis, University of Pennsylvania.

Edward A. Strecker, M.D., F.A.C.P., Consultant-in-Chief, Institute of the Pennsylvania Hospital; Professor of Psychiatry, University of Pennsylvania School of Medicine.

William D. Stroud, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; Cardiologist, Pennsylvania Hospital; Cardiologist and Director of the Heart Station, Bryn Mawr Hospital; Physician-in-Chief, Cardiovascular Service, Abington Memorial Hospital.

Max M. Strumia, M.D., Director of Laboratory of Clinical Pathology, Bryn Mawr Hospital; Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine.

James M. Surver, M.D., F.A.C.S., Associate in Surgery, Jefferson Medical College of Philadelphia.

Charles Swalm, M.D., Assistant Coroner's Physician, City of Philadelphia.

Paul Swenson, M.D., Professor of Radiology, Jefferson Medical College of Philadelphia.
Gerrit Toennies, Ph.D., Organic Chemist, Lankenau Hospital Research Institute.
Louis N. Tuft, M.D., Assistant Professor of Medicine and Chief of Allergy Clinic, Temple University School of Medicine.
Henry Tumen, M.D., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.
J. Vastine, M.D., Professor of Radiology, Woman's Medical College of Pennsylvania.
Matthew Walzer, M.D., Chief of Allergy Clinic, Jewish Hospital, Brooklyn, N. Y.
Edward Weiss, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.
William White, M.D., Research Fellow in Surgery, University of Pennsylvania School of Medicine.
Bernard P. Widmann, M.D., Professor of Radiology, University of Pennsylvania Graduate School of Medicine.
George Willauer, M.D., F.A.C.S., Associate in Surgery, Jefferson Medical College of Philadelphia.
Elizabeth Wilson, M.D., Assistant Coroner's Physician, City of Philadelphia.
Carroll S. Wright, M.D., Professor of Dermatology and Syphilology, Temple University School of Medicine; Associate Professor of Dermatology and Syphilology, University of Pennsylvania Graduate School of Medicine.
Thomas H. Wright, M.D., Clinical Director, Department for Mental and Nervous Diseases, Pennsylvania Hospital; Instructor in Psychiatry, University of Pennsylvania School of Medicine.
Joseph Yaskin, M.D., Professor of Neurology, University of Pennsylvania Graduate School of Medicine.

### Outline of Course

Monday, November 8.

*Psychosomatic Medicine*

Edward Weiss, M.D., F.A.C.P., In Charge
Temple University School of Medicine
3400 N. Broad St.
X-Ray Museum, Sixth Floor

A.M.

9:00–11:00 Psychosomatic Conference.
Cardiac Neurosis (Neurocirculatory Asthenia); Hypertension. Functional Indigestion; Cardiospasm; and Peptic Ulcer.
Dr. Weiss and Dr. English.

11:00–12:00 Low Back Pain; Panel Discussion.
Dr. Chamberlain, Dr. Moore, Dr. Scott and Dr. Weiss.

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Monday, November 8.

*Allergy*

Merle M. Miller, M.D., F.A.C.P., In Charge
Graduate Hospital of the University of Pennsylvania
19th and Lombard Sts.
North Lecture Room

P.M.

2:00– 2:20 Principles of Allergy. Physiological Pathology of the Allergic State.
Dr. Tuft.

2:20– 3:10 Seasonal Pollinosis. Treatment of Hay Fever—Evaluation of Different Methods.
Dr. Spain.

3:10– 4:00 Gastrointestinal Allergy. Experimental Alimentary Allergy. Clinical Evaluation. (Motion Pictures.)
Dr. Walzer.
4:00– 4:20 Bronchial Asthma. Pathology.
Dr. Eiman.
4:20– 5:00 Diagnosis and Treatment. Demonstration of Skin Testing. Passive Transfer.
Dr. Miller.

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Tuesday, November 9.

*Syphilis*

NORMAN R. INGRAHAM, JR., M.D., In Charge
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
34th and Spruce Sts.

A.M.
9:00– 9:10 Introductory Remarks: The Public Health Importance of Syphilis in War Times.
Dr. Ingraham.
9:10– 9:50 The Problem of Falsely Positive Reactions in the Serology of Syphilis (Lecture and Discussion).
Dr. Kolmer.
9:50–10:30 Blindness Caused by Syphilis (Lantern Slides, Illustrative Case Records and Charts).
Dr. Klauder.
10:30–11:25 Standard Versus Intensive Treatment of Syphilis: Military and Civilian Applications (Lecture and Discussion).
Dr. Stokes and Dr. Beerman.
11:25–12:00 Treatment Reactions to Antisyphilitic Therapy.
Dr. Wright.

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Tuesday, November 9.

*Blood Diseases*

MAX M. STRUMIA, M.D., In Charge
BRYN MAWR HOSPITAL
Bryn Mawr, Pa.
Assembly Room, Third Floor

P.M.
2:00– 3:00 The Hemolytic Diseases.
Dr. Strumia.
3:00– 4:00 The Metabolism of Hemoglobin.
Dr. Karr.
4:00– 5:00 Reticuloendotheliosis.
Dr. Strumia.

Dr. Blake and Dr. Chornock will assist in the discussion and demonstration.

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Wednesday, November 10.

*Cardiovascular Diseases*

WILLIAM D. STROUD, M.D., F.A.C.P., In Charge
PENNSYLVANIA HOSPITAL
8th and Spruce Sts.
(Detailed outline yet to come)

A.M.
9:00–12:00

Wednesday, November 10.

*Peripheral Vascular Disorders*

DAVID W. KRAMER, M.D., F.A.C.P., In Charge

JEFFERSON MEDICAL COLLEGE

1025 Walnut St.

Society Room

P.M.

2:00– 2:15 Evaluation of Various Methods of Investigating Peripheral Circulation.
Dr. Kramer.

2:15– 2:30 Fluorescein as a Means of Investigating the Status of Peripheral Circulation.
Dr. Abramson.

2:30– 2:45 Periarteritis Nodosa; Allergic Influences.
Dr. Hobart A. Reimann and Dr. Price.

2:45– 3:00 Endarteritis Obliterans.
Dr. Kramer.

3:00– 3:15 Phlebitis—Acute and Chronic; Treatment.
Dr. Willauer.

3:15– 3:30 Freezing Therapy and Anesthesia for Gangrene.
Dr. Surver.

3:30– 3:45 Amputation for Gangrene: When, Where and How?
Dr. Shallow.

3:45– 4:00 Ganglionectomy for Peripheral Vascular Disorders: Indications and Choice of Procedure.
Dr. Jaeger.

4:00– 4:15 Blood and Plasma in Treatment of Chronic Leg Ulcers.
Dr. Naide.

4:15– 5:00 Evaluation of the Various Newer Methods in Treatment of Peripheral Vascular Disorders.
Dr. Kramer.

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Thursday, November 11.

*Arthritis and Related Conditions*

RALPH PEMBERTON, M.D., F.A.C.P., In Charge

ABINGTON MEMORIAL HOSPITAL

Abington, Pa.

A.M.

9:00–12:00

SYMPOSIUM

1. Statistical Factors.
2. Pathology.
3. Physiologic Disturbances Involved.
4. Clinical Presentation of Cases, with Emphasis on Diagnostic Methods and Treatment.
5. Round Table Discussion.
   Dr. Pemberton, Dr. Bach and Dr. Scull.

Thursday, November 11.

*Gonorrhea*

PAUL R. LEBERMAN, LT., (MC-V-S), U.S.N.R., and HARRY E. MORTON, SC.D.
U. S. NAVAL HOSPITAL
16th St. and Pattison Ave.
Barracks A

P.M.
2:00– 5:00 Introduction.
Applied Anatomy and Histology of Lower Urinary Tract.
Gonococcus—Pathology of Gonorrhea.
Influence of Anatomic Structures.
Clinical Course of Gonorrhea.
Dr. Leberman.

Neisseria Gonorrheae.
Morphology of the Gonococcus.
Staining Reactions.
Biology of the Gonococcus (Susceptibility to temperature above body temperature. Relation to fever therapy).
Susceptibility to Temperatures below Body Temperature.
Precautions to Be Taken for Preservation of Specimens from Time of Collection until Cultured.
Susceptibility to Weak Alkali (Microscopic and macroscopic tests).
Susceptibility to Disinfectant Action of Chemicals.
Importance of 10% CO2 and Moisture for Maximum Growth.
Cultivation.
Media Used for Satisfactory Growth of the Gonococcus.
Methods for Cultivating under 10% $CO_2$.
Comparison of the Efficiency of Culturing versus Smear Technique for Detecting the Gonococcus.
Morphology of Gonococcus Colonies.
Biochemical Reactions.
Oxidase Test.
Fermentation Tests.
Pathogenicity for Man and Other Animals.
Dr. Morton.

Diagnosis of Gonorrhea.
Technique of Gram Stain.
Technique of Culture Procedures.
Two Glass Test.
Considerations of Non-Gonorrheal Urethral Discharges.
Cause of Local Symptoms.
Dr. Leberman.

Treatment.
Local Medication.
Chemotherapy.
Tests of Cure.
Complications and Treatment Thereof.
General Principles and Application of Artificial Hyperpyrexia (Kettering Hypertherm Cabinet).
Dr. Leberman.

Management of Venereal Diseases in the Tropics.
Lymphopathia Venereum.
Dr. Mann.

Prevention and Control of Gonorrhea.
Prophylaxis.
Instruction to Patient.
Coöperating Agencies for Control.
1. LaFollette-Bulwinker Bill for the Control of Venereal Disease.
2. Mann Act.
3. May Bill.
Dr. Leberman.

Round Table Discussion.
Dr. Leberman.

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Friday, November 12.

*Respiratory Diseases*

HOBART A. REIMANN, M.D., and LOUIS H. CLERF, M.D., F.A.C.P., In Charge

JEFFERSON HOSPITAL

10th and Walnut Sts.

Clinical Amphitheater

A.M.

9:00–10:30 Acute Diseases of the Upper and Lower Respiratory Tract.
Dr. Reimann.

10:30–12:00 Chronic Diseases of the Respiratory Tract.
Dr. Clerf.

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Friday, November 12.

*Tuberculosis*

DAVID A. COOPER, M.D., F.A.C.P., In Charge

PHILADELPHIA GENERAL HOSPITAL

34th St. below Spruce St.

Lecture Room, First Floor, Tuberculosis Division

P.M.

2:00– 5:00 Tuberculin as a Tool in Tuberculosis Control.
Dr. Seibert.
Nutrition in Tuberculosis.
Dr. Getz.
Natural Resistance to Tuberculosis.
Dr. Lurie.
Surgery in Tuberculosis.
Dr. Lewis.
Clinical Conference.
Dr. Cooper and Staff.

Saturday, November 13.

*Gastrointestinal Diseases*

HENRY L. BOCKUS, M.D., F.A.C.P., In Charge

GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

19th and Lombard Sts.

North Lecture Room

A.M.

9:00–10:00 SECONDARY GASTROINTESTINAL DISORDERS

Gastrointestinal Reactions in Depression.
Dr. Yaskin.
Abdominal Symptoms in Diabetes.
Dr. Beardwood.
Gastrointestinal Allergy.
Dr. Miller.

10:00–11:00 ROUND TABLE CONFERENCE—Dr. Bockus, Leader.

The Clinical Application of Liver Function Tests in:
1. Jaundice.
Dr. Tumen.
2. Cirrhosis of the Liver.
Dr. Monaghan.
3. Cardiac Disorders.
Dr. Griffith.

11:00–12:00 GASTRO-ENTEROLOGIC CONFERENCE: Case Problems.

Medical Aspects.
Dr. Bockus.
Roentgenologic Aspects.
Dr. Finkelstein.
Surgical Aspects.
Dr. Lee.

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Monday, November 15.

*Chemotherapy*

HARRISON F. FLIPPIN, M.D., F.A.C.P., In Charge

PHILADELPHIA GENERAL HOSPITAL

34th St. below Spruce St.

Surgical Amphitheater

A.M.

9:00–12:00 PANEL DISCUSSION: Chemotherapy.

Sulfamerazine and Sulfamethazine; Introductory Remarks.
Dr. Flippin.
Sulfamerazine vs. Sulfadiazine—Clinical Evaluation.
Dr. Gefter.
Sulfonamides—Pharmacology.
Dr. Reinhold.
Sulfonamides and Penicillin—Laboratory Studies.
Dr. Lockwood.
Penicillin—Clinical Evaluation.
Dr. White.

Monday, November 15.

*Diagnostic Roentgenology*

BERNARD P. WIDMANN, M.D., In Charge

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

34th and Spruce Sts.

X-Ray Lecture Room, Fourth Floor

P.M.

2:00– 5:00 Roentgenologic Problems in Diseases of the Chest.
Dr. Kornblum.
Roentgenologic Consideration of Non-Surgical Lesions of the Breast.
Dr. Vastine.
Roentgenologic Aspects of:
(a) Platybasia.
(b) Low Back Pain.
Dr. Chamberlain.
Roentgenologic Problems in Bone Disease.
Dr. Swenson.
Roentgenology of the Urinary Tract.
Dr. Pendergrass.
Roentgenology of the Heart.
Dr. Ostrum.
Roentgenologic Problems in Diseases of the Gastrointestinal Tract.
Dr. Widmann.

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Tuesday, November 16.

*Psychiatry*

LAUREN H. SMITH, M.D., F.A.C.P., In Charge

THE INSTITUTE OF THE PENNSYLVANIA HOSPITAL

111 N. 49th St.

Auditorium

A.M.

9:00–12:00 The Wish to Fall Ill (Case Seminar).
Dr. Bond.
The Fundamentals of Clinical Psychiatry in the Community.
Dr. Strecker.
The Use of the Electroencephalogram as a Diagnostic Aid.
Dr. Hughes.
The Use of Physiological Adjuncts in Therapy.
Dr. Palmer.
The Status of Shock Therapy.
Dr. Smith and Dr. Wright.
The Use of the Psychotherapeutic Interview in General Medicine.
Dr. Appel.

Tuesday, November 16.

*Metabolic Problems*

JOSEPH T. BEARDWOOD, JR., M.D., F.A.C.P., In Charge

GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

19th and Lombard Sts.

(Detailed outline yet to come)

P.M.
2:00– 5:00

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Wednesday, November 17.

*Tropical Medicine*

WM. HARVEY PERKINS, M.D., F.A.C.P., In Charge

JEFFERSON MEDICAL COLLEGE

1025 Walnut St.

Auditorium

A.M.
9:00–12:00 Tropical Diseases of Potential Danger to This Country.
Dr. Perkins.
National and International Defenses against Tropical Diseases.
Dr. Dunnahoo.
Immunization in Tropical Diseases.
Dr. Kneedler.

P.M.
2:00– 5:00 Diagnosis of Important Tropical Diseases.
Dr. Sawitz and Staff; Dr. Morgan and Staff.

*To be followed by laboratory demonstrations and discussion.*

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Thursday, November 18.

*Tumors*

STANLEY P. REIMANN, M.D., F.A.C.P., In Charge

THE LANKENAU HOSPITAL

Girard and Corinthian Avenues

Doctors' Library

A.M.
9:00–12:00

1. Carcinoma of the Stomach.
Dr. Engel.
2. Problems of Transplantation of Normal and Tumor Tissue.
Dr. Briggs.
3. Principles of Reconstruction after Removal of Tumors.
Dr. May.
4. Carcinoma of the Rectum.
Dr. Martin.
5. Sulfur Compounds and Growth.
Dr. Toennies, Dr. Medes and Dr. Bennett.
6. A Few Growth Problems Solvable by Tissue Culture.
Dr. Royle.

Thursday, November 18.

*Legal Medicine*

HERBERT M. GODDARD, M.D., In Charge

PHILADELPHIA CITY MORGUE

13th and Wood Sts.

| P.M. | |
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| 2:00– 3:00 | Cardiac Traumatism, Industrial and Accidental.<br>a. The usual types of cardiac traumatism seen in industry.<br>b. The relationship of coronary artery disease and trauma.<br>Dr. Gouley. |
| 3:00– 3:30 | Sudden Death Due to Hemorrhagic Necrosis of the Adrenal Glands Associated with Meningococcic Infection.<br>Dr. Wilson. |
| 3:30– 4:30 | Demonstration of Fresh Pathologic Material from Cases of Sudden Death.<br>Dr. Swalm, Dr. Wilson and Dr. Gouley. |

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Friday, November 19.

REGIONAL MEETING

OF THE

AMERICAN COLLEGE OF PHYSICIANS

| A.M. | |
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| 9:30–12:00 | Medical Clinics.<br>Hospital of the University of Pennsylvania, O. H. Perry Pepper, M.D., F.A.C.P., In Charge. |
| P.M. | |
| 1:00 | Buffet Luncheon.<br>College Headquarters. |
| 2:00– 5:00 | General Session.<br>Papers by eminent authorities, both Service and Civilian.<br>(Detailed program later; also announcement of place of meeting.) |
| 6:30 | Cocktail Party and Dinner-Meeting.<br>Benjamin Franklin Hotel. |